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SERUM AND URINE AMINO ACIDS IN INFANTILE TOXICOSIS

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THE proteins of the serum in cases of toxicosis† have been extensively studied since 1924. Electrophoretic studies by Hallman and associates,[1] by Imperato,[2] and by Choremis and Moschidis[3] showed a marked or moderate increase of alpha globulin, especially the α_2 fraction and a decrease of albumin during the acute stage of the dehydration. In some cases there was also an increase in the gamma globulin.

We have been interested in studying the free amino acids of the serum and of the urine by paper chromatography in infantile toxicosis. Ströder and associates,[4] have studied the serum amino acids of 2 cases of toxicosis by the iodiometric method and have found an increased amount (15 to 18 mg. of NH_2-N per cent). In 14 cases of uncomplicated diarrhea the level of amino acids was found to be normal. In 1955, Chaptal and associates[5] published their results of chemical determinations of serum polypeptides and amino acids on "several infants" suffering from toxicosis. There was an increase of polypeptides (5 to 12 mg. per cent) and of amino acids (6 to 11 mg. per cent) in the serum. No significant hyperaminoacidemia was found by Schreier[6] in 1955 in 23 patients with uncomplicated diarrhea. In 5 infants with severe diarrhea there was a significant increase in the plasma amino acids level which could not be accounted for by the change in hematocrit. "Outspoken hyperaminoacidemia" was found in 2 children with severe toxicosis by microbiological techniques and column chromatography.

Loeb and Engelen,[7] in a paper published after the completion of the present research, have studied by the Folin colorimetric method the urinary excretion of amino acids in 31 cases of toxicosis due to diarrhea and have found slight variations from the normal. The paper chromatography of the amino acids of the urine presented no abnormalities in 11 studied cases and no constant relationship was observed between the values of the chemical determination and the number of spots on the chromatogram. The total nitrogen deficit sometimes doubled during the first 48 hours. In

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†Referred to in the European literature as the state of severe dehydration from diarrhea or other infections with collapse and loss of consciousness.

4 cases of toxicosis due to infections other than gastrointestinal, they observed a high aminoaciduria. They concluded that there is apparently an increased nitrogen catabolism in all cases and that the metabolism of amino acids is not very disturbed in cases of toxicosis due to diarrhea. In the cases of toxicosis of other origin they conclude that "the aminoacid metabolism is profoundly disturbed."

MATERIAL AND METHODS

Forty-four infants from 3 to 10 months of age and a child 23 months old were divided into three groups according to the severity of their condition as estimated by the clinical examination and the laboratory data:

Group A was composed of 12 pretoxic infants.

Group B was composed of 15 cases of moderate severity.

Group C was composed of 18 cases of severe toxicosis.

The history previous to the present illness was approximately the same in all cases, with diarrhea and vomiting for 1 to 9 days. Fever was present in 14 cases and symptoms of otitis media in 3 cases. All the patients were hospitalized in the Pediatric Clinic of Athens University during the summer and fall of 1956.

All infants, except 5, were artificially fed. All of them had been full-term babies with an average birth weight of 3,000 grams, except 2 prematurely born with a weight of 2,280 and 2,300 grams, respectively.

Treatment was started on admission and after obtaining a sample of blood for amino acid chromatography, hematocrit and total serum protein determination. Sodium chloride, 0.85 per cent solution, was administered parenterally with 5 per cent glucose in water as well as M/6 sodium lactate solution. Darrow's solution was administered orally on the second and third days. Blood or plasma transfusions and amino acid solutions were not given at all to these patients. Parental fluid therapy, as a rule, lasted for 24 to 36 hours. Then the infants were fed with powered skimmed milk and from the seventh to tenth day with half-skim powdered milk. Antibiotics (Aureomycin, Terramycin, Chloromycetin, and neomycin) were given for a period of 5 to 10 days.

Full recovery occurred on the average, within 3 to 5 days in the first group, within 5 to 8 days in the second and third groups. Three patients belonging to the third group succumbed.

Bidimensional chromatography was applied: first dimension, phenol-water; second dimension, pyridine-amyl alcohol-water. Five-hundredths milliliter protein-free serum and a quantity of urine equivalent to 500 γ of total nitrogen (determined by the Kjeldahl method) were used for each chromatogram. The urine specimens were collected 12 to 24 hours after admission of the patients when the infant was almost completely hydrated, as the urine collected before hydration was too concentrated.

Another urine chromatogram was done 8 days after admission on 27 of the patients, who had in the meantime fully recovered.

Two other groups of infants were studied for comparison:

The one was composed of 12 normal infants, 4 to 15 months old; the

second contained 12 cases of uncomplicated gastroenteritis, without dehydration, in infants 4 to 13 months of age.

The total serum protein was determined by the Robertson method and the hematocrit by the Wintrobe method.

RESULTS

Normal Infants.—The serum chromatogram revealed the presence of 5 to 7 amino acids: glycine, glutamic acid, alanine, threonine, valine, leucine, and tyrosine. In the urine, 8 to 10 amino acids were present: glycine, glutamic acid, alanine, threonine, valine, leucine, lysine, arginine, histidine, and serine.

Cases of Uncomplicated Gastroenteritis.—The serum and urine amino acids were identical to those observed in the normal infants group.

Cases of Toxicosis.—

Serum amino acids: Six to eight amino acids were found in the serum chromatograms and they were qualitatively the same as in the group of normal infants. An attempt for quantitative estimation, done by the comparison of the size of the spots and the intensity of their color, gave us the impression that the amount of amino acids of the serum of toxic infants was not elevated, but it is well known that this method of estimation is not very exact (Fig. 1).

Urine amino acids: A marked aminoaciduria was observed in all the infants studied. The aminoaciduria was found to be in close relationship with the gravity of the clinical picture and less to the degree of dehydration, as far as this may be estimated by the total serum protein and the hematocrit.

In group A (pretoxic infants), 14 to 16 amino acids were present in the urine.

In group B (moderate severity) 15 to 17 amino acids were present.

In group C (severe cases), 15 to 18 amino acids were present in the urine.

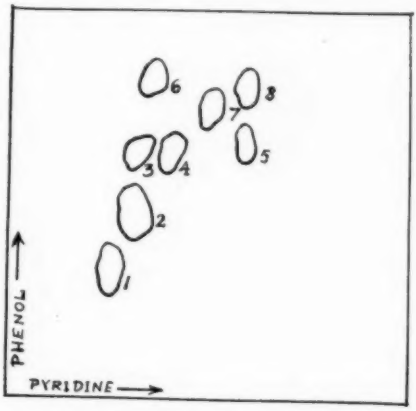

Fig. 1.—Chromatogram of the serum of an infant suffering from toxicosis on admission. *1*, Glutamic acid; *2*, glycine; *3*, alanine; *4*, threonine; *5*, tyrosine; *6*, arginine; *7*, valine; *8*, leucine.

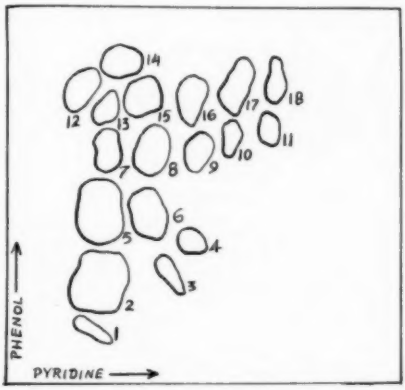

Fig. 2.—Chromatogram of the urine of an infant suffering from toxicosis on admission. *1*, Asparaginic acid; *2*, glutamic acid; *3*, cysteic acid; *4*, taurine; *5*, glycine; *6*, serine; *7*, alanine; *8*, threonine; *9*, α-aminobutyric acid; *10*, tyrosine; *11*, tryptophane; *12*, lysine; *13*, methionine; *14*, arginine; *15*, histidine; *16*, valine; *17*, leucine; *18*, phenylalanine.

TABLE I. RESULTS OF URINE CHROMATOGRAPHY

	PRETOXIC CASES				CASES OF MODERATE SEVERITY				SEVERE CASES			
	ON ADMISSION		8 DAYS AFTER ADMISSION		ON ADMISSION		8 DAYS AFTER ADMISSION		ON ADMISSION		8 DAYS AFTER ADMISSION	
Number of cases studied	12		4		15		12		18		11	
AMINOACIDS	NO. OF CASES IN WHICH PRESENT	RANGE OF AMOUNT	NO. OF CASES IN WHICH PRESENT	RANGE OF AMOUNT	NO. OF CASES IN WHICH PRESENT	RANGE OF AMOUNT	NO. OF CASES IN WHICH PRESENT	RANGE OF AMOUNT	NO. OF CASES IN WHICH PRESENT	RANGE OF AMOUNT	NO. OF CASES IN WHICH PRESENT	RANGE OF AMOUNT
Lysine	12	1+ to 3+	4	1+	15	1+ to 3+	12	1+	18	1+ to 2+	11	1+
Arginine	12	1+ to 2+	4	1+	15	1+ to 2+	12	1+	18	1+ to 2+	11	1+
Histidine	12	1+ to 2+	0	-	15	1+ to 2+	2	1+	17	1+ to 2+	7	1+
Valine	12	1+ to 2+	4	1+	15	1+ to 2+	12	1+	18	1+ to 2+	10	1+
Leucine	12	1+ to 2+	4	1+	15	1+ to 2+	12	1+	18	1+	11	1+
Tryptophane	5	1+	0	-	11	1+	0	-	9	1+	2	1+
Tyrosine	12	1+	1	1+	15	1+	10	1+	18	1+	4	1+
α-aminobutyric acid	11	1+ to 2+	0	-	11	1+ to 2+	0	-	16	1+	1*	1+
Threonine	12	1+ to 2+	4	1+	15	1+ to 2+	12	1+ to 2+	18	1+ to 2+	1*	1+
Methionine	8	1+ to 2+	0	-	11	1+ to 2+	0	-	15	1+	1*	1+
Alanine	12	1+ to 2+	4	1+	15	1+ to 2+	12	1+ to 2+	18	1+ to 2+	11	1+ to 2+
Taurine	12	1+	2	1+	15	1+	9	1+	18	1+	11	1+
Serine	12	1+ to 2+	4	1+ to 2+	15	1+ to 3+	12	1+ to 2+	18	1+ to 3+	11	1+ to 2+
Glutamic acid	12	1+ to 3+	4	1+ to 2+	15	1+ to 3+	12	1+ to 2+	18	1+ to 4+	11	1+ to 2+
Asparaginic acid	11	1+	3	1+	13	1+	7	1+	18	1+ to 2+	6	1+
Glycine	11	1+ to 3+	2	1+	12	1+ to 3+	8	1+	16	1+ to 4+	6	1+
Cysteic acid	9	1+	0	-	14	1+	10	1+	15	1+ to 2+	6	1+
Phenylalanine	3	1+	0	-	11	1+	0	-	13	1+ to 2+	0	-

*Condition still severe.

The following amino acids were found: glycine, alanine, histidine, taurine, glutamic acid, arginine, leucine, valine, lysine, tyrosine, threonine, serine, cysteic acid, asparaginic acid, tryptophane, phenylalanine, methionine, and α-aminobutyric acid. The excretion of tryptophane, methionine, phenylalanine, which are not found in normal urine, was more marked in groups B and C (Fig. 2 and Table I).

The individual excretion of each amino acid as well as the total aminoaciduria was markedly increased.

In the urine there were also present faint to heavy traces of albumin, casts, and occasionally traces of sugar and red cells.

The total serum proteins were found to be 6.55 to 8.86 Gm. per cent of the 25 patients tested. The hematocrit was 32 to 44 per cent. There was not always present a stable correlation between the severity of the clinical condition and the dehydration, on one hand, and the values of total serum proteins and the hematocrit, on the other. Different preexisting factors, as hunger hypoproteinemia, anemia, increased toxic breakdown of protein, defective protein synthesis, and protein losses from the blood to the tissues by a mechanism similar to surgical shock (the increased permeability of capillary membranes)[8-10] were responsible for this lack of correlation.

Urine amino acids 8 days after admission: The urine chromatogram of the infants of the group A (pretoxic patients) was again normal 8 days after admission.

In the groups B and C the number of amino acids in the urine was increased to 12-14 with the following amino acids being found: glycine, glutamic acid, alanine, histidine, taurine, tyrosine, arginine, leucine, valine, lysine, threonine, serine, asparaginic acid, and tryptophane.

DISCUSSION

There is an increased catabolism of proteins in infantile toxicosis. The frank aminoaciduria observed in toxicosis could be explained by the hemoconcentration and a disturbed deaminating and transaminating function of the liver. The alterations of the hepatic cells are well known.[11] Also an exaggerated catabolism of proteins may be partly responsible for the aminoaciduria. The finding by paper chromatography that there was not an increased amount of aminoacidemia in the cases of our study, in connection with the well-known alterations of renal function in toxicosis, made us think that the observed aminoaciduria in toxicosis is probably, for the most part, of renal origin. No amino acid clearance test in toxicosis could be done because of the severity of the condition of the patients.

SUMMARY

The serum and urine amino acids of 45 infants and babies suffering from toxicosis were studied by paper chromatography. In the serum there was no deviation from the normal. In the urine there were observed 14 to 18 amino acids estimated as an increased amount for each one. Eight days after admission there was still an augmented excretion of amino acids (12 to 14) in the urine. It is

believed that the renal damages in toxicosis must be incriminated for the aminoaciduria observed.

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Medical Advertising Is Still a Problem

When Rowland Hill invented the penny postage stamp, and put in circulation the smallest paper money in existence, he little thought of the evil uses to which his admirable idea would be turned. He little anticipated that ingenious gentlemen, who roam about seeking whom they may devour would, through its agency, manage to live upon the public in princely style, their whole stock in trade being an advertisement in the paper!

A RETIRED PHYSICIAN, whose sands of life have nearly run out, discovered, while in the East Indies, a Certain Cure for Consumption, Asthma, Bronchitis, Coughs, Colds, and general debility. The remedy was discovered by him when his only child, a daughter, was given up to die. He had heard much of the wonderful restorative and healing qualities of preparations made from the East Indian Hemp, and the thought occurred to him that he might make a remedy for his child. He studied hard, and succeeded in realising his wishes. His child was cured, and is now alive and well. . He has since administered the wonderful remedy to thousands of sufferers in all parts of the world, and he has never failed in making them completely healthy and happy. Wishing to do as much good as possible, he will send to such of the afflicted fellow being as request it, this recipe, with full and explicit directions for making it up and successfully using it. He requires each applicant to enclose him six stamps—one to be returned as postage on the recipe, and remainder to be applied to the payment of this advertisement. Address H. JAMES, M.D., 14, Cecil-street, Strand. . . . The proper punishment for this gentleman, whose "sands of life are nearly run," would be a sound outward application of good English Hemp to his own person.

From an Editorial in BRITISH MEDICAL JOURNAL,
March 6, 1858

BRONCHOPULMONARY SEQUESTRATION IN INFANCY AND CHILDHOOD

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BRONCHOPULMONARY sequestration is usually considered to be the association of an anomalous artery with a dissociated or sequestrated bronchopulmonary mass. Although developmental in origin, relatively little has appeared in the pediatric literature concerning this problem. Bronchopulmonary sequestration is usually limited to a lower lobe. It is the purpose of this communication to present two cases occurring in children, one of which involved the upper lobe and was associated with congenital absence of the pericardium.

CASE REPORT

CASE 1.—S. G. S., a 3-year-old white girl, was admitted to Welborn Memorial Baptist Hospital because of physical findings compatible with a right pleural effusion. Two weeks previously she had developed a febrile illness with sore throat and vomiting. On antimicrobial therapy she improved temporarily but subsequently developed intermittent high fever, dyspnea, and right chest pain which failed to respond to continued treatment. There was a past history of recurrent respiratory infection treated successfully with antibiotics.

On admission the patient appeared acutely rather than chronically ill, and exhibited tachypnea and an expiratory grunt. There was a definite pallor but no cyanosis or clubbing of the digits. There were flatness to percussion and diminution of breath sounds over the right lung base. Examination of the heart was not remarkable except for tachycardia. Admission hemogram revealed a moderate anemia and a polymorphonuclear leukocytosis of 20,150 per cubic millimeter. Tuberculin and histoplasmin skin tests were negative. Roentgenograms of the chest showed an ill-defined opacity involving the lower one-half of the right lung field with a well-demarcated mass at the right hilar area (Fig. 1). A radiologic diagnosis of empyema was made.

Thoracentesis yielded 110 ml. of purulent fluid, but all smears and cultures for pyogenic organisms, acid-fast bacilli, and fungi were negative. Subsequently, four of eleven thoracenteses revealed small amounts of fluid. On tetracycline therapy the patient became afebrile in one week, and subsequent roentgenograms demonstrated gradual resolution of the opacity at the right base. However, at the time of discharge one month later a cystic area at the right base containing an air-fluid level was still present (Fig. 2).

On prophylactic doses of tetracycline the patient remained afebrile and asymptomatic, but the lesion in the right lung persisted, leading to a brief readmission three weeks later for bronchoscopy which was nonrevealing. As there had been no change in the appearance of the cystic area in the right chest, she was admitted for the

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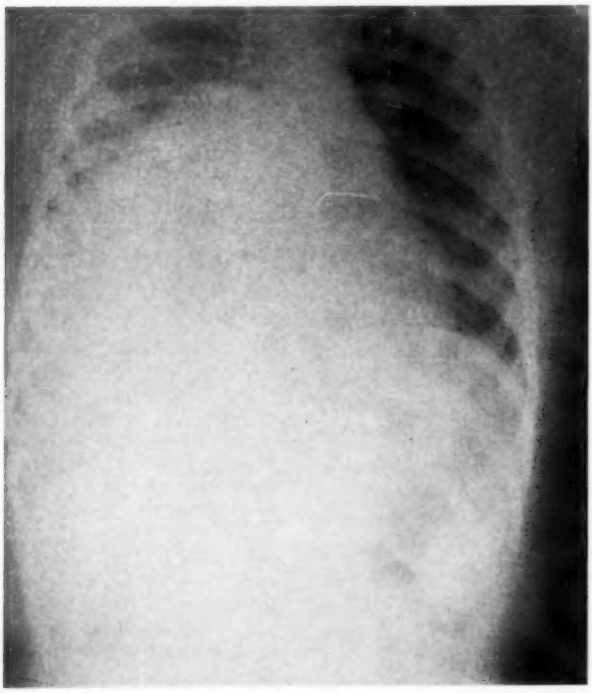

Fig. 1.—Case 1. Showing pleural fluid and mass in right hilar area on admission.

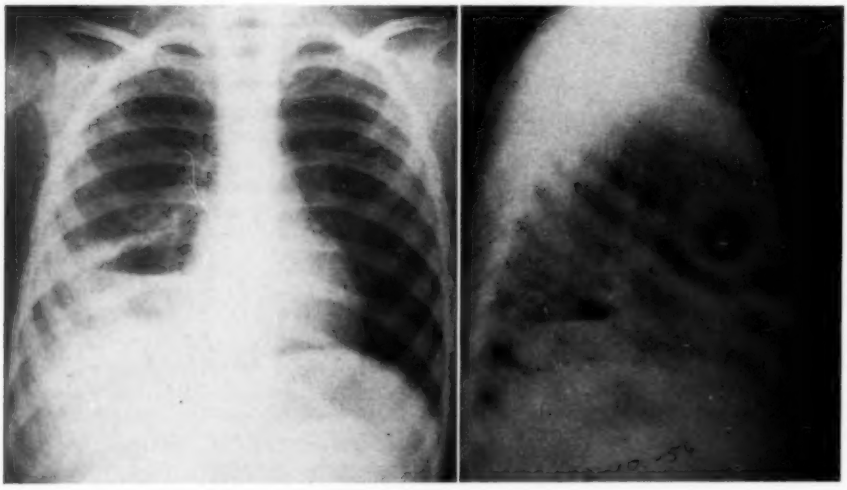

Fig. 2.—Case 1. One month after admission, showing air-fluid accumulation at base of right lung.

third time one month later and an exploratory right thoracotomy was performed.* On entering the chest, the pleural space was found to be obliterated by previous inflammatory reaction. As the right lower lobe was freed from adhesions one large and four smaller arteries were seen to course through the diaphragm and extend via the inferior pulmonary ligament to the involved lung. After ligation of these vessels the lower lobe was removed and was found to include a multiloculated cavity 5 cm. in diameter and a smaller satellite cavity, both of which were filled with a thick mucoid material. Microscopically the cysts were lined by a low columnar epithelium resembling the lining of a terminal bronchus. The surrounding tissue was fibrous, congested, and infiltrated with round cells. The postoperative course was uneventful.

When seen four months later, the patient was clinically well and a roentgenogram of the chest was essentially normal (Fig. 3).

Case 2.—B. J. A., a 7½-year-old white boy, was first seen with a history of cough of one month's duration and a mass presenting in the left anterolateral portion of the neck dating from 1 year of age. The mass had enlarged consistent with body growth but no obstructive symptoms had appeared. There was no history of recurrent pulmonary infection. Positive physical findings included a 3.5 by 4.5 cm. cystic nonpulsating mass in the left side of the neck, overlying the left lobe of a normally palpable thyroid gland and extending downward toward the thoracic inlet. The trachea was displaced slightly to the right but the lung fields were clear, and examination of the heart was normal. Tuberculin and histoplasmin skin tests were negative, as was a complete hemogram. Roentgenogram of the chest revealed a radiopaque, sharply demarcated, ovoid mass in the superior left mediastinum, which, on fluoroscopy, was noted to cause deviation of both the trachea and esophagus to the right. The lung fields were clear. The heart was not enlarged but exhibited a peculiar, almost boot-shaped configuration. Electrocardiogram was normal. The possibility of a cystic hygroma originating in the neck and extending into the mediastinum was entertained. After clearing of the respiratory infection, he was admitted to Welborn Memorial Baptist Hospital where the cystic lesion of the neck on excision was found to be a branchial cleft cyst.

The patient was admitted to Vanderbilt University Hospital six weeks later, where the mediastinal lesion was again visualized on roentgenograms and by fluoroscopy. Initially these findings were felt to represent enlarged inflammatory mediastinal nodes with pleuropericardial adhesions producing the peculiar configuration of the heart (Fig. 4). A fluid-filled cyst was also considered. Hemogram, urinalysis, and sedimentation rate were normal. Tuberculin, histoplasmin, coccidioidin, and blastomycin skin tests were negative.

An exploratory thoracotomy* was performed through the third left interspace. The left mediastinal pleura and the entire pericardium were found to be absent. The heart appeared normal and no thrill was palpable. The aorta descended to the right of the spine and the ligamentum arteriosum was located in its normal position so that no vascular ring was produced. Examination of the left lung revealed a normal lower lobe. Contained in a wedge-shaped cleft in the upper lobe, however, was a 4 by 5 cm. firm, beefy-red, airless segment of pulmonary tissue. The ectopia was entirely free of surrounding lung tissue and was thought to conform to the anterior segment of the upper lobe. Its only attachment was a small pedicle of

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Fig. 3.—Case 1. Four months postoperatively, revealing complete clearing of right lung.

Fig. 4.—Case 2. On admission, demonstrating the enlargement of the left superior mediastinum and abnormal cardiac silhouette.

fibrous tissue, and its blood supply consisted of a branch from the pulmonary artery, plus a bronchial artery, and a vein running superiorly to the left innominate vein. No bronchial communication could be identified. The sequestrum was removed and on section was found to contain a cyst, 2 cm. in diameter, filled with mucoid material. This cyst was lined with respiratory epithelium and, in the walls, bronchial glands were noted interposed between cartilaginous rings. Adjacent to the wall many large blood vessels were noted. Several smaller cysts, lying in fetal-appearing lung tissue, surrounded the larger central cyst. No inflammatory reaction was noted.

The patient made an uneventful postoperative recovery and has remained completely asymptomatic since discharge.

DISCUSSION

Embryology.—It is generally agreed that bronchopulmonary sequestration is of congenital origin, and may be intralobar or extralobar, presumably depending on the stage of embryonic development at which it originates. Gallagher and co-workers[1] have grouped prevailing theories concerning development of the anomaly into four categories—mechanical, traction, vascular insufficiency, and idiopathic—and have discussed the points for and against each. The hypothesis that has received most favor is that of vascular traction, suggested by Pryce.[2, 3] This theory considers the primary fault to be in the development of an abnormally located artery and the associated pulmonary anomaly to be a complication or secondary effect. Blood vessels occasionally differentiate in abnormal locations in the primitive splanchnic plexus of the embryo but usually atrophy. However, for reasons unknown, such an anomalous artery may persist. Such an artery may then exert traction on the developing lung bud it supplies and detach the bud from the remainder of the bronchial tree, producing a sequestrum.

There is considerable speculation, however, concerning the role of an anomalous artery in producing the pulmonary ectopia since anomalous systemic arterial supply to normal pulmonary tissue has been demonstrated repeatedly and reported in the literature as early as 1777. Wall and Lucido[4] favor the concept that sequestration results from "fractioning" of a developing lung bud which subsequently seeks its own blood supply by attracting adjacent embryonic blood vessels of systemic origin. Beneke[5] has observed that ectopic tissue may obtain a vascular supply from its vicinity if the malformation occurs early enough in embryonic development. Rosenthal's[6] case suggests that such a pulmonary artery may cause sequestration of portion of the lower lobe and in itself become separated from the aorta.

Regardless of the exact mechanism, the sequence of events is most likely to occur in the region of the primitive diaphragm. The aberrant arteries most frequently arise from the lower thoracic or upper abdominal aorta and commonly traverse the inferior pulmonary ligament. Pryce[2, 3] found that the anomalous arteries, although of systemic origin, frequently resembled pulmonary arteries in that their walls were more elastic than muscular. Some were found to appear systemic on the aortic side and pulmonic on the lung side.[7] In any event, such arteries subject to systemicarterial pressure often exhibit atheromatous degeneration.[2] In the majority of

cases, venous drainage is by way of the normal pulmonary venous system. Occasionally, however, anomalous venous drainage has been observed, as was true in Case 2.

Several significant differences between extralobar and intralobar sequestration have been pointed out by Pryce[2]:

1. Extralobar sequestration shows a marked left-sided preponderance, only three of forty cases having occurred on the right side.

2. Venous drainage from an extralobar sequestrum frequently is to the hemiazygos, with intralobar sequestrum usually to the pulmonary vein.

3. Extralobar sequestration commonly is associated with a diaphragmatic hernia. This has not been noted with intralobar pulmonary sequestration.

The left preponderance of extralobar sequestration suggests a later embryonic origin when the expanding pleural sacs envelop the pericardium. The absence of the left mediastinal pleura and pericardium associated with the pulmonary ectopia in Case 2 provides evidence to support this.

Pathology.—In the case of intralobar sequestration, the sequestrum lies within a pulmonary lobe; and although it may seem to correspond to a particular segment, it is poorly demarcated from surrounding normal lung tissue. Such a sequestrum most commonly is located in the posteromedial portion of a lower lobe in proximity to the origin of the aberrant artery supplying it, as in Case 1. Pryce[2] has classified the gross pathology as follows: (1) a large cyst in the sequestered area (50 per cent), (2) a polycystic mass (40 per cent), or (3) a sequestered mass containing bronchi that branch parallel to the artery. The bronchial or cystic elements usually are completely disassociated from the normal bronchial tree. The bronchi, although usually blind, may have minute connections with the normal bronchial tree, permitting the entrance of air or opaque oil into the cyst.[8] Various workers have suggested that the area of the lungs supplied by an accessory artery coming from the aorta is nonfunctioning. Although there is experimental evidence to the effect that the sequestered segment is no more likely to become infected than the normal lung,[9] there is considerable pathologic and clinical evidence that such areas are unduly predisposed to infection.[1, 8, 13] Lemmon and co-workers,[10] using colored vinyl acetate, demonstrated the distribution of the anomalous artery to be about the cyst and confined to the sequestered segment of the lobe, whereas the pulmonary artery supplied aerated segments of the lobe. The anomalous vessel invariably lies in the center of the diseased area where structural disorganization of advanced degree is seen.[11] This association appears to lend further support to the concept of an etiologic relation between the vessel and the changes of sequestration.

In the case of extralobar sequestration the lesion is anatomically separated from the adjacent lung, although otherwise the gross and microscopic pathology is similar to intralobar sequestra. Extralobar sequestra apparently are seldom infected.

Case 1 represents an example of intralobar pulmonary sequestration.

Case 2 represents extralobar pulmonary sequestration as evidenced by anatomical separation from adjacent lung and the location in the left side of the chest, anomalous venous drainage, absence of infection, and associated pleuropericardial defect.

Clinical Aspects.—As one might suspect, intralobar sequestra usually are unaccompanied by symptoms, but this is not true in the case of intralobar sequestra where recurrent infection is the rule and usually begins at an early age.

In intralobar bronchopulmonary sequestration, the average age of onset of symptoms in cases compiled by Pryce[2, 3] was 19 years and the average age at surgery was 26 years. Sex distribution was approximately equal. In 47 cases the right side was involved in 20, and the left in 27. The incidence of the condition in one institution as reported by Pryce was 1.7 per cent among 270 pulmonary resections or excisions. The symptoms of intralobar pulmonary sequestration are those of infection, including fever, chills, cough, and pleuritic pain. The diagnosis may be confused with pneumonia, pleurisy, empyema, bronchiectasis, or lung abscess. Tuberculosis in the sequestered segment has been reported in an occasional case.[18]

The roentgenographic appearance in asymptomatic cases may suggest congenital cystic disease of the lung or perhaps bronchiectasis. Cytic lesions may contain air-fluid levels (Case 1). Infected lesions are most apt to be confused with empyema or lung abscess by the radiologist. Wyman[12] states that the presence of a lower lobe density with a fingerlike appendage extending toward the aorta should suggest the correct diagnosis. Aortography or planography may be helpful but the diagnosis must be suspected beforehand. Bronchoscopy may be of diagnostic aid in the occasional case. The systemic reaction of the patient in most cases seems to be less than would be anticipated from the extent of the pulmonary consolidation observed radiographically.

Antibiotic therapy produces only temporary remission from symptoms, and infection invariably recurs. Bronchoscopic aspiration and postural drainage are of little or no avail unless the lesion communicated with the bronchial tree.

Definitive treatment is surgical and consists of extirpation of the diseased tissue. In extralobar sequestration the lesion may be excised without disturbing the adjacent normal lung. In intralobar pulmonary sequestration lobectomy is indicated, particularly since, in childhood, growth of the lung by means of the addition of more alveolar units continues for several years.[14] The surgeon should recall, however, that in lower lobe lesions severance of the anomalous arteries transversing the interior pulmonary ligament or diaphragm may result in uncontrollable hemorrhage.

Congenital Absence of the Pericardium.—Rusby and Sellors[15] have published a comprehensive review covering the historical and embryological aspects of congenital absence of the pericardium. With the exception of their case and the two reported by Ladd[16] and Dahl,[17] respectively, the other 79 cases reported in the literature up to the time of their reports were chance findings discovered at post-mortem examination. As in Case

2 of this report, the case reported by Rusby and Sellors[15] was associated with an extralobar pulmonary sequestration. Congenital absence of the pericardium may be asymptomatic and compatible with life.

SUMMARY

Bronchopulmonary sequestration is a congenital pulmonary ectopia or sequestration associated with an anomalous artery, usually originating from the aorta. Two cases, one intralobar and the other extralobar in type, occurring in children are reported. The latter was associated with congenital absence of the pericardium; both patients were cured by surgical extirpation of the involved segment. A selected review of the literature emphasizing the various theories as to embryological origin, pathology, and clinical manifestations of bronchopulmonary sequestration is presented.

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SERUM BILIRUBIN LEVELS IN THE NEWBORN INFANT AND THEIR RELATION TO CLINICAL ICTERUS AND LIVER FUNCTION STUDIES

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THE problem of jaundice in the newborn infant has recently been of increasing concern to many workers. The simple explanation has been that fetal oxygen tension is low, resulting in insufficient aeration and compensatory increase in erythrocytes. Concomitantly, there occurs a high hemoglobin value as well as immature nucleated red cells. Within the first two weeks of life, the excessive red cells are partially destroyed, and an increase of bilirubin in the blood plasma occurs, resulting in the so-called physiological icterus of the newborn.[1] A more profound understanding and better interpretation of the phenomena involved was given by Weech.[2] He illustrated that previous workers had failed to demonstrate a relationship between the amount of hemoglobin destroyed and the intensity of bilirubinemia and suggested the immature liver function as one possible variable factor. More recently, the temporarily impaired bilirubin excretory function of the newborn's liver has again been emphasized as a large factor in the production of intense jaundice.[3]

Danoff and associates[4] have recently shown that the elevated indirect bilirubin which is sometimes present in the blood of the newborn infant and which is responsible for the condition known as physiological jaundice is due to a deficiency of the enzyme glucuronyl transferase in the liver during the neonatal period. It is this enzyme that is responsible for the conversion of the indirect-reacting bilirubin to the direct-reacting bilirubin through the formation of the glucuronide of bilirubin. Not until this function has become normal will the jaundice disappear.

In the more profound disturbances such as biliary atresia, erythroblastosis, inspissated bile ducts, infectious hepatitis and obstructive jaundice due to miscellaneous causes, bilirubin levels of the serum have been determined and liver function tests have been studied to differentiate the causes of the jaundice.[5] The authors used these studies to determine the optimum treatment, surgical or medical, and advised liver function studies with serial bilirubin levels and blood grouping date to establish the etiology of jaundice.

Serum bilirubin levels during the newborn period have been well studied by Hsia and associates.[6] However, no correlation was established between the serum bilirubin level and the appearance of clinical jaundice as manifested by icteric discoloration of the skin and sclerae. It has also been

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noted that factors other than the bilirubin level might influence the appearance of pigment in the skin, as, for example, the state of hydration. Christensen[7] has described an affinity of the skin for bilirubin in cases of myxedema.

Other factors which influence the appearance of jaundice have been suggested by Allen and Diamond[8] in their observations that jaundice is not present in erythroblastotic infants immediately after birth even though the bilirubin level may be as high as 8 mg. per cent. They discuss the possibility of bilirubin not having been deposited in the cells of the skin at birth and also the possibility of light being a factor in causing jaundice to become apparent. This latter theory is substantiated in part by the absence of apparent pigmentation in the folds of skin not exposed to light and areas of skin shielded from light by adhesive tape.

It was therefore deemed advisable to study, in cases of so-called physiological icterus, the level of serum bilirubin, and to attempt to correlate this with the degree of hemolysis as evidenced by fall in hemoglobin and with the appearance of clinical jaundice. It was also proposed to attempt to determine in these cases whether the impaired bilirubin excretory function of the liver was accompanied by other manifestations of liver insufficiency as evidenced by abnormal liver function studies. Since bilirubin and liver function studies were repeated within forty-eight to seventy-two hours, it was attempted to ascertain whether high serum bilirubin levels could produce damage to the liver cells in so short a period of time, resulting in abnormal liver function studies.

METHODS

Twenty-five newborn, full-term infants were studied. Venous blood was obtained by femoral puncture for the serum bilirubin and liver function tests twenty-four to forty-eight hours after birth. At the same time, capillary blood was obtained for the hemoglobin and hematocrit determinations. Forty-eight to seventy-two hours later the above determinations were repeated. During this period, clinical observations were made to detect obvious jaundice as manifested by skin and scleral icterus, and attempts were made to correlate these with the liver function studies and with the change in hemoglobin and hematocrit findings.

The infants studied were presumably normal infants, and cases of biliary obstruction and erythroblastosis were excluded. They were either breast fed or given a routine evaporated milk, water, and carbohydrate formula. In all instances the infants showed the usual weight changes and were discharged from the hospital as normal infants.

Total bilirubin was performed on 0.1 ml. serum according to the method of Malloy and Evelyn.[9] Only total bilirubin determinations were performed, since it has long been known that in the newborn child who presents no evidence of liver disease the indirect bilirubin is by far the larger component of the total bilirubin. The recent work of Danoff and associates[4] also lends support to the above assumption. Cephalin flocculation was done on 0.1 ml. of serum according to the method of Hanger.[10] Thymol turbidity was done on 0.1 ml. of serum according to the method of MacLagen.[11] Total and free cholesterol

was performed on 0.4 ml. of serum according to the method of Kaye.[12] Total proteins and albumin and globulin fractionations were performed on 0.3 ml. of serum according to the procedure of Kimbrick and Blonstein.[13] Alkaline phosphatase was done on 0.5 ml. of serum according to the procedure of Bodansky.[14]

RESULTS

The results are listed in two tables. In Table I are the liver function, hematocrit, and hemoglobin studies on those newborn infants with a total bilirubin of less than 5 mg. per cent, while Table II contains the results on those newborn infants whose total bilirubin was greater than 5 mg. per cent.

Of those cases which had a bilirubin level of less than 5 mg. per cent, only one showed slight clinical evidence of jaundice. This was Case 2, where the total bilirubin rose to 4.3 mg. per cent. It is suggestive that factors other than serum bilirubin alone determine the clinical manifestation of jaundice. This is borne out by such findings as Case 19, where there was a moderate jaundice with a bilirubin level of 9.1 mg. per cent and Case 21 where there was no jaundice with a bilirubin level of 11.1 mg. per cent.

Neither does the fall in hemoglobin and hematocrit alone fully explain the presence or absence of clinical jaundice. Thus, Case 10 showed a drop of hemoglobin from 19.2 to 12.3 Gm. and a drop in hematocrit from 60 to 40 per cent with no apparent jaundice; whereas Case 14 revealed a drop in hemoglobin from 16.2 to 13.6 mg. and a drop in hematocrit from 49 to 45 per cent. And with this moderate fall there appeared severe jaundice.

There appeared to be no strict correlation between the bilirubin level and the drop in the hemoglobin. Thus, Case 10 showed a drop in hemoglobin from 19.2 to 12.3 Gm., and the bilirubin concurrently dropped instead of rising, as might be expected, dropping from 2.7 to 1.9 mg. per cent. Conversely, in Case 21 we found no drop in hemoglobin, and the bilirubin level rose from 6.1 to 11.1 mg. per cent. Similarly, Case 24 showed no change in hemoglobin and a rise in bilirubin from 3.4 to 9.5 mg. per cent.

The concentration of bilirubin in the serum is usually lower in cases of physiological jaundice than in erythroblastosis or in obstructive jaundice. In our series only one case had a bilirubin level of over 20 mg. per cent. This infant (Case 15) was a premature infant who suffered a traumatic delivery and had extensive ecchymoses over the thorax and extremities. Exchange transfusion was performed to lower the bilirubin level, and no clinical evidence of kernicterus or brain damage was evident up to the time of discharge from the hospital.

The results obtained in the studies of thymol turbidity, total proteins, albumin globulin ratios, and alkaline phosphatase were essentially normal. No evidence of liver function impairment could be obtained from the above results.

The cephalin flocculation tests were found to be abnormal in some instances. By our standards we assume an abnormal finding wherever the test showed 2 plus or greater. The cephalin flocculation tests were abnormal in the same degree of frequency whether the bilirubin level was

TABLE I. LIVER FUNCTION STUDIES ON NEWBORN INFANTS WITH A TOTAL BILIRUBIN OF MORE THAN 5 MG. PER CENT

CASE NO.	DEGREE OF CLINICAL JAUNDICE	AGE (DAYS)	HGB. (GM./ 100 ML.)	HCT. (%)	TOTAL BILIRUBIN (MG. %)	CEPH. FLOCC. 24 HR. 48 HR.	THYMOL TURBIDITY (UNITS)	TOTAL CHOLEST. (MG. %)	FREE CHOLEST. (MG. %)	% FREE CHOLEST.	TOTAL PROTEIN (GM. %)	ALBUMIN (GM. %)	GLOBULIN (GM. %)	ALB./GLOB.	ALKALINE PHOSPHAT. (BODANSKY UNITS)
NORMAL VALUES			14.5-20.0	42-63	0.2-1.0	0-2+	0-5	135-290		22-32	6.0-8.0	3.6-6.0	2.0-2.5	1.5-3.0	1.5-6.5
1	0	1	20.0	63	1.2	0 1+	1.2	116	24.2	20.9					2.5
		4	19.2	59	3.4	0 0	1.3	158	56.2	35.5					1.6
2	+	1	15.8	48	3.1	0 1+	0.9	134	29.6	22.1					
		2	17.7	57	4.3	0 1+	1.8	150	36.0	24.0					
3	0	1	15.3	5.0	3.4	0 0	3.0	108	27.4	25.3	6.50	4.70	1.80	2.6	2.5
		4	14.8	4.3	2.0	0 1+	2.6	177	37.0	20.9	6.60	3.88	2.72	1.5	2.4
4	0	1	15.8	49	1.1	0 0	2.0	112	26.8	23.9	6.82	4.20	2.62	1.6	4.4
		3			3.0	0 2+	2.1	143	58.6	41.0	6.02	3.58	2.44	1.4	4.2
5	0	1	18.7	62	2.0	1+ 2+	1.8	73	28.8	39.4	7.24	5.28	1.96	2.6	1.3
		4			0.85	0 1+	1.6	104	23.5	22.6	6.45	4.52	1.93	2.3	3.6
6	0	1	17.9	57	1.2	0 0	1.2	110	34.4	31.3	7.52	5.10	2.42	2.1	
		3	19.2	60	0.85	3+ 4+	1.0	113	45.2	40.0	7.31	4.88	2.43	2.0	

7	0	1	20.2	68	1.6	1+ 2+	1.0	77	21.0	28.0	7.70	5.10	2.60	1.9	1.5
		3	16.2	55	1.6	2+ 4+	0.8	120	61.3	51.1	7.24	5.26	1.90	2.6	2.0
8	0	1	18.7	52	1.2	1+ 2+	1.6	85	56.0	65.9	6.45	4.30	2.15	1.9	1.2
		4	18.0	50	0.85	2+ 3+	1.0	123	58.1	47.2	6.65	4.38	2.27	1.9	1.5
9	0	1	17.0	54	0.89	2+ 3+	1.6	108	31.3	28.9	6.19	3.85	2.61	1.3	8.0
		3	16.7	52	0.85	1+ 2+	2.4	154	63.6	41.3	6.50	4.52	1.98	2.2	6.1
10	0	1	19.2	60	2.7	0+ 1+	0.5	100	20.8	20.8	7.24	5.10	2.14	2.3	
		3	12.3	40	1.9	0+ 1+	1.8	139	33.5	23.4	7.75	5.70	2.05	2.7	
11	0	1	19.7	62	2.5	2+ 3+	0.8	92	35.8	38.9	6.19	4.12	2.07	2.0	
		3	18.9	59	0.85	2+ 3+	1.2	163	31.6	19.4	5.25	3.25	2.00	1.6	
12	0	1	17.2	59	1.6	0 0	1.0	100	24.5	24.5	8.26	6.00	2.26	2.6	
		2	11.5	36	3.4	0 1+	2.0	125	31.2	25.0	7.75	5.70	2.05	2.7	

TABLE II. LIVER FUNCTION STUDIES ON NEWBORN INFANTS WITH A TOTAL BILIRUBIN OF MORE THAN 5 MG. PER CENT

CASE NO.	DEGREE OF CLINICAL JAUNDICE	AGE (DAYS)	HGB. (GM./ 100 ML.)	HCT. (%)	TOTAL BILIRUBIN (MG. %)	CEPH. FLOCC. 24 HR. 48 HR.	THYMOL TURBIDITY (UNITS)	TOTAL CHOLEST. (MG. %)	FREE CHOLEST. (MG. %)	% FREE CHOLEST.	TOTAL PROTEIN (GM. %)	ALBUMIN (GM. %)	GLOBULIN (GM. %)	ALB. / GLOB.	ALKALINE PHOSPHAT. (BODANSKY UNITS)
13	++	1	16.7	51	8.1	1+ 3+	0.75	101	43.0	43.0	7.35	4.35	3.00	1.5	
		2	16.0	54	8.1	0 1+	1.3	200	55.1	27.6	7.83	5.18	2.65	2.0	
14	+++	1	16.2	49	17.3	1+ 2+	2.2	134	43.8	40.1	7.11	5.01	2.10	2.4	2.8
		5	13.6	45	14.8	0+ 2+	1.8	220	55.3	25.1	6.15	4.26	1.89	2.1	3.4
15	+++	2	15.3	50	23.4	0 ±	0.72	162	72.5	44.8	6.20	4.26	1.94	2.1	5.4
		5	12.3	43	20.2	0 1+	1.1	257	77.2	30.0	5.40	3.87	1.53	2.5	4.9
16	+	1	18.7	59	5.0	0 0	0.71	107	22.2	20.8	6.90	4.12	2.78	1.5	5.1
		3	14.8	43	5.5	0 0	0.50	100	24.0	24.0	6.45	4.12	2.33	1.7	5.5
17	++	1	16.7	65	3.1	0 0	0.58	108	26.0	24.0	6.54	3.80	2.74	1.4	5.8
		2	15.7	57	12.9	0 +	1.2	180	70.0	38.9	5.85	3.85	2.00	1.9	6.5
18	+	1	20.2	62	4.2	0 0	0.75	110	26.3	23.7	6.39	4.02	2.37	1.6	
		3	18.2	57	10.7	0 ±	0.74	133	41.3	31.0	5.50	3.78	1.72	2.2	
19	++	1	20.2	57	3.1	2+ 3+	0.86	120	38.1	31.7	6.50	4.24	2.36	1.8	
		3	18.2	53	9.1	2+ 4+	2.3	200	53.8	26.9					

20	+	1	18.2	55	4.0	1+ 2+	2.3	75	13.9	18.5	6.65	4.66	1.99	2.3	3.2
		4	17.7	50	5.1	0 2+	1.1	103	40.0	38.8	6.30	4.24	2.06	2.0	3.6
21	0	1	18.7	56	6.1	0 0	3.2	114	28.0	24.5	6.82	4.24	2.58	1.6	2.1
		3	18.7	59	11.1	0 0	1.4	165	78.9	47.8	5.85	3.80	2.05	1.8	1.5
22	+	1	19.0	53	3.6	0 2+	0.76	141	36.7	26.0	5.17	3.70	1.47	2.5	5.2
		4			12.0	0 0	3.2	175	49.1	28.0	5.17	2.98	2.19	1.3	5.5
23	+	1	19.2	59	1.9	0 3+	0.80	117	26.7	22.8	6.65	4.24	2.41	1.7	4.9
		3			10.7	0 0	2.0	197	77.5	39.8	6.50	4.12	2.38	1.7	4.2
24	0	1	19.7	56	3.4	0 1+	1.6	122	43.6	35.7	7.70	5.28	2.42	2.1	
		3	19.7	60	9.5	0 0	2.3	126	46.2	36.6	7.50	5.26	2.24	2.3	
25	0	1	20.5	72	2.4	0 2+	0.92	106	38.0	36.0					
		2	19.7	65	6.7	0 1+	1.0	118	46.0	39.1					

elevated or not. For example, Case 6 showed 3 and 4 plus cephalin flocculation with only 0.85 mg. per cent bilirubin. Conversely, Case 15, with the highest bilirubin levels of 23.4 and 20.2 mg. per cent, had a normal cephalin flocculation. Of the cases where the bilirubin level was less than 5 mg. per cent, seven of the twelve cases had cephalin flocculation tests of 2 plus or more. In the infants where the bilirubin level was 5 mg. per cent or higher, the cephalin flocculation tests were 2 plus or higher in seven of the thirteen cases. Therefore, it cannot be concluded that an elevated cephalin flocculation is related in any way to evidence of hepatic dysfunction produced by an elevated bilirubin.

An interesting point was observed concerning total serum cholesterol levels. These tended to run lower during the first two days of life than after the second day of life. If 135 mg. per cent is considered as the lower limit of normal in the adult, it is observed that in only two cases was a value greater than 135 mg. per cent obtained during the first two days of life. Forty-eight hours after birth the total cholesterol levels rose, the greater number falling above 135 mg. per cent. This is illustrated in Fig. 1.

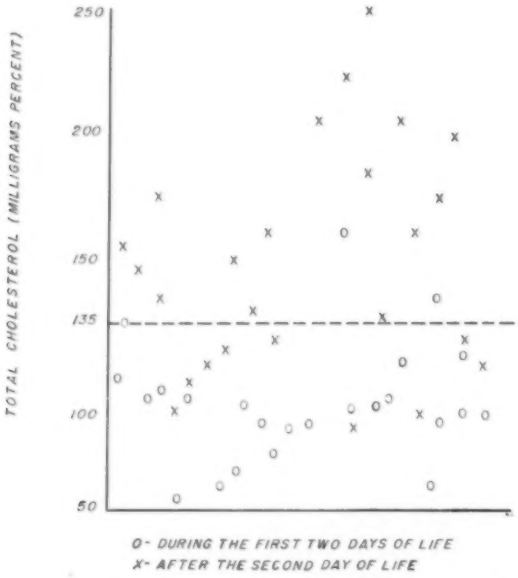

Fig. 1.—A comparison of the total serum cholesterol during the first two days of life with total serum cholesterol after the second day of life.

It may be that in the newborn child there exists a deficiency in the enzyme system necessary for the endogenous synthesis of cholesterol from two carbon units. Only after the second day of life are the above deficiencies rectified in most children. In some infants, a longer period of time after birth may be needed for the blood cholesterol to reach normal levels.

SUMMARY

Hemoglobin, hematocrit, and blood liver function studies were performed on twenty-five normal newborn infants during the first two days of life and repeated forty-eight to seventy-two hours later.

Attempts were made to correlate total serum bilirubin with liver function studies, changes in the hemoglobin and hematocrit level and the degree of clinical icterus. No correlation could be established between the total serum bilirubin levels and the blood liver function studies. Even after a period of forty-eight to seventy-two hours had elapsed in cases where the blood bilirubin level was elevated, there were no signs of hepatic dysfunction as evidenced by abnormal liver function studies. Not all cases showed a significant drop in hemoglobin and hematocrit associated with a rise in serum bilirubin. Conversely, some cases showed an appreciable rise in bilirubin with little or no change in hemoglobin or hematocrit. In not all instances could the total serum bilirubin be directly correlated with the extent of clinical jaundice. In some cases jaundice was noted where the bilirubin level was only moderately elevated, whereas in other cases there was no jaundice with appreciably elevated serum bilirubin.

When total serum cholesterol studies were performed on infants during the first or second day of life, the results tended to be significantly lower than the level obtained on the same infant on the third to fifth day of life.

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FLORA OF THE UMBILICAL STUMP

2,479 Cultures

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THIS study was undertaken to determine the flora found on routine cultures of the umbilical cord and cord-cutaneous junction in the newborn period to provide a basis for interpretation of culture reports taken from the umbilical area. Cultures were taken weekly over a 2½-year period preceded by a 30-day period of daily cultures of every infant and followed by a 30-day period of biweekly cultures of every infant in the Newborn Nursery of Brooke Army Hospital. As this study did not follow an epidemic of pyoderma in the newborn, the authors feel their findings are of interest to the epidemiologists in interpreting data found during or following the appearance of pyoderma in the nursery and verify Jellard's[1] findings that the cord is a major reservoir of *Staphylococcus aureus* in the newborn nursery, which in turn emphasizes the need to prevent cross-contamination by strains already existent in a hospital.

PLAN OF STUDY

This study was divided into three major phases. The first phase was to obtain daily cultures of the cord-cutaneous junction of every infant at Brooke Army Hospital for 30 days. Phase II cultures were taken at weekly intervals for a period of 130 weeks. The bacteriology of Phases I and II was performed by the Bacteriology Department at Brooke Army Hospital. The final, or third, phase consisted of biweekly cord cultures of all infants in the nursery for 30 days. The bacteriology for this phase was performed at the U. S. Army Surgical Research Laboratory at Brooke Army Medical Center.

Phase I.—A total of 1,159 daily cultures of the cord-cutaneous junction were taken by one of us (J. P. F.) on 211 infants in the Newborn Nursery of Brooke Army Hospital for a 30-day period, July 7 through Aug. 6, 1955. Cultures were taken with a sterile dry applicator between 7:30 and 8:00 A.M. daily and planted within the next 30 minutes. Specimens were plated directly on blood agar, eosin methylene blue agar (EMB), and thioglycolate broth. These were incubated for a 24-hour period and those cultures showing no plate growth were streaked from broth to blood agar and EMB plates. A coagulase test was performed on the Staphylococci. These were then subcultured to 7.5 salt agar

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and mannitol broth. Beta hemolytic Streptococci were identified by colonial morphology and the catalase test. Gram-negative bacilli were identified by appropriate biochemical tests.

Phase II.—Phase II varied from Phase I only in that the selection of cases was random by the charge nurse and limited to 2- to 5-day-old infants. These cultures were taken by the charge nurse and sent by regular messenger through normal channels and were planted when received by the laboratory. Bacteriology for Phase II cultures was the same as for Phase I cultures.

Phase III.—Cultures were taken as in Phase I, twice weekly (Tuesday and Thursday) rather than daily. Every infant present in the nursery was cultured on these two days for a 30-day period, and recultured when returned for his well-baby check at 30 days of age. Cultures were planted within a 30-minute period from the time they were collected. The swab specimen was streaked on blood agar base, EMB, milk salt agar, and phenol red mannite salt agar. *Staphylococcus aureus* colonies were subsequently picked to milk salt agar and allowed to incubate at room temperature for several days. This was to allow the developing of maximal carotenoid pigmentation, and to permit the possible production of phospholipase as evidenced by an opalescent halo.[2] All Staphylococci were tested for coagulase activity. Coagulase-positive organisms were typed by use of the Blair method.[3] Early in the bacteriological study of Phase III cultures it became evident that a combination of coagulase activity and phospholipase zoning on egg-yolk media by carotenoid-pigmented Staphylococci indicated a propensity for phage typing. Ultimately this criterion was used to determine which Staphylococci should be typed. Beta hemolytic Streptococci were delimited as Group A or D on the basis of chemical tolerance tests and sensitivity to bacitracin-impregnated discs. Alpha hemolytic Streptococci were differentiated from Pneumococci on the basis of bile solubility and growth insensitivity to ethyl hydrocupreine hydrochloride discs. Gram-negative organisms were either of the coliform variety, identified by IMVIC reactions, or Proteus which was identified on the basis of rapid hydrolysis of urea. No Salmonella or Shigella was encountered in Phase III bacteriological studies. Providencia paracolobactrum was isolated on two occasions and typed with B and O serum as somatic Group B (types 11 through 20) Providencia. Of interest is the fact that no Pseudomonas varieties were isolated in Phase III.

RESULTS

Phase I.—This study included 214 patients. Three were excluded as one was cultured only on the ninth day of life, the day the series started, and two died in the first two days of life, leaving 211 patients. Of these 211 patients, 210 had coagulase-positive *Staphylococcus aureus* cultured from the cord-cutaneous junction at least once during their nursery stay. Those cultured on the day of delivery were frequently found to have no growth on the culture media. The day of delivery was defined for this study to include up to midnight on the day of birth. As cultures were taken at 8:00 A.M., this would include only those infants less than 8 hours old. Therefore, for the purposes of this study, the first day of life would be over 8 and under 36 hours of age.

TABLE I. PHASE I—CULTURES BY DAY OF LIFE

ORGANISMS	DELIVERY DATE (%)	DAY 1 (%)	DAY 2 (%)	DAY 3 (%)	DAY 4 (%)	DAY 5 (%)	DAY 6 (%)
Staphylococcus aureus coagulase positive	5	65	85	81	86	81	80
Staphylococcus aureus coagulase negative		0.6	0.6	0.5			2
Staphylococcus albus	6	14	8	8	4	3	4
Streptococcus, alpha hemolytic		0.6	0.6				0.5
Streptococcus, beta hemolytic		24	41	56	61	62	70
Escherichia coli		12	17	25	28	27	19
Klebsiella-Aerobacter Gr.		7	10	10	7	11	5
Proteus Sp.	3	5	12	15	8	11	10
Pseudomonas Sp.		12	14	10	12	9	6
No growth	85	17	1		0.5	0.5	3
Total Number of Cultures	65	174	179	187	188	184	182

Table I indicates the type of bacteria found by day of life. It will be noted that of 65 cultured on day of delivery (under 8 hours of age) 85 per cent revealed no growth, 6 per cent had *Staphylococcus albus,* 5 per cent *Staphylococcus aureus,* and 3 per cent a Proteus species. By the second day of life the incidence of coagulase-positive *Staphylococcus aureus* reached a high level and remained approximately at this level for the remainder of the hospital stay. The presence of a high incidence of beta hemolytic Streptococci was also noted.

Of these 211 patients, 176 returned to the Out-Patient Clinic for a 1-month check. Of the 176, 167 had no significant skin lesion, or if they had had any skin problem during the month it cleared without any therapy. Nine problem patients were seen either during this month's period, or at the well-baby check at 30 days. Four of these nine grew coagulase-positive *Staphylococcus aureus* from either the umbilical area or a skin lesion. Three were treated with penicillin and one was treated with bacitracin ointment locally. The remaining five were found to have beta Streptococci. These five were treated with penicillin and cleared without incident.

Phase II.—Routine cultures were taken weekly on 5 to 10 patients chosen at random in the nursery between the ages of 2 and 5 days from Sept. 2, 1955, through Feb. 25, 1958. A total of 1,031 cultures was taken in this series. The incidence of *Staphylococcus aureus* remained high throughout the entire period and compared well with the incidence of *Staphylococcus aureus* found in the intensive culture period of July as shown in Table II and the second part of Fig. 1. Although the incidence of beta Streptococcus was less than in the intensive

TABLE II. PHASE II—WEEKLY SAMPLE CULTURES

	(%)
Staphylococcus aureus, coagulase positive	82
Staphylococcus aureus, coagulase negative	0.9
Staphylococcus albus	3
Streptococcus, beta hemolytic	36
Escherichia coli	28
Klebsiella-Aerobacter Gr.	22
Proteus Sp.	3
Pseudomonas Sp.	0.8
Total Number of Cultures	1,031

culture period, this organism was found in a high percentage of the cords. The ratio of *E. coli* remained approximately the same between the two series as did *Staphylococcus albus*. Proteus and Pseudomonas sp., however, did not appear as frequently.

quency of occurrence between *Staphylococcus albus* and *aureus* at the 1-month check compared to the first week of life. The relative incidence of organisms found at the 1-month check in the umbilical area is listed in Table IV.

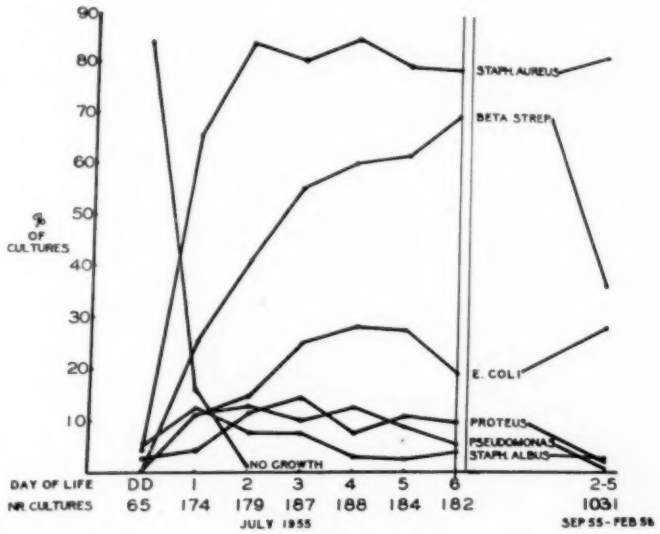

Fig. 1.—Cultures of the cord-cutaneous junction by day of life with the organisms indicated in percentage of cultures taken.

Phase III.—A total of 273 cultures on 144 patients was obtained in Phase III. Infants less than 8 hours old were omitted from this group. The cultures were taken, again between 7:30 and 8:00 A.M., on all infants in the nursery, including those born the previous day up to and including midnight. The findings are recorded in Table III and in Fig. 2. It will be noted that the fifth- and sixth-day cultures were omitted in Chart II as they were so few in number. The *Staphylococcus aureus* appears in approximately the same order of frequency in all three phases. It is of interest to note a reversal in the order of fre-

Of these 144 infants cultured, a follow-up was obtained on 132. Ninety-eight of the 132 were recultured at 1 month of age; 32 were examined and no culture obtained, while telephone assurance that there had been no skin problem was accepted on the remaining two. Only two of the 132 had significant skin findings; that is, findings that could remotely be considered a possible infection. These two had pustules, one of which contained the 52/42B/44A/81 *Staphylococcus aureus* in the pustules. The other, who had numerous pinpoint lesions, was not cultured and was treated locally without antibiotics.

TABLE III. PHASE III—CULTURES BY DAY OF LIFE

ORGANISMS	DAY 1 (%)	DAY 2 (%)	DAY 3 (%)	DAY 4 (%)	DAY 5 (%)	DAY 6 (%)
Staphylococcus aureus coagulase positive	44	67	69	85	91	88
Staphylococcus aureus coagulase negative	6					
Staphylococcus albus and/or *citreus*	38	45	20	25	9	13
Staphylococcus aurantiacus			3			
Streptococcus, alpha hemolytic	6	5	9	4		
Streptococcus, beta hemolytic (Groups other than Group D)	25	25	14	44	9	25
Enterococcus (Group D)	6	9	11	15		13
Escherichia coli	13	27	46	50	73	13
Klebsiella-Aerobacter Gr.	6	22	26	29	64	25
Proteus Sp.	6	3	9	4		13
Providencia Sp.	13	2				
Corynebacterium Sp.		7				
No growth	25	3				
Total Number of Cultures	16	44	35	48	11	8

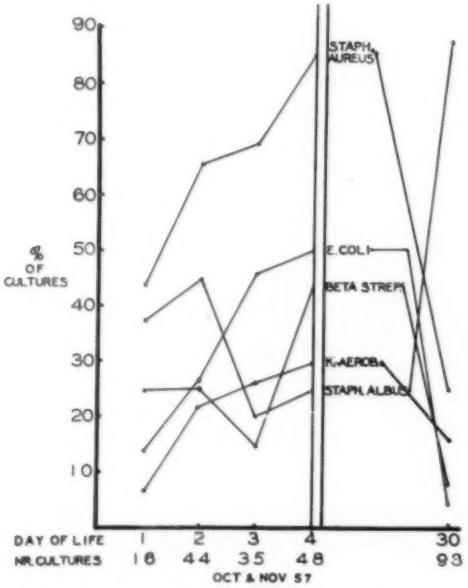

FIG. 2.—Cultures of the cord-cutaneous junction by day of life in Phase III with the most frequent organisms indicated in percentage of cultures taken.

TABLE IV. FOLLOW-UP CULTURES AT 30 DAYS OF LIFE

	(%)
Staphylococcus aureus, coagulase positive	28
Staphylococcus aureus, coagulase negative	20
Staphylococcus albus and/or *citreus*	87
Streptococcus, alpha hemolytic	3
Streptococcus, beta hemolytic (Groups other than Group D)	8
Enterococcus (Group D)	10
Escherichia coli	4
Klebsiella-Aerobacter Gr.	17
Proteus Sp.	11
Corynebacterium Sp.	1
B. subtilis	2
No growth	3
Total Number of Cultures	98

TABLE V. PHAGE TYPE DISTRIBUTION IN 106 NEWBORN INFANTS

	ALONE	COMBINED WITH		TOTAL
		NONTYPABLE	47/53/54/75/77/va4/76	
52/42B/44A/81	14	26	2	42
47/53/54/75/77/Va4/76	3			3
7	4			4
7 plus 44A			1	1
7 plus 47C			1	1
47C plus 52A			1	1
Nontypable	53		1	54
	74	26	6	106

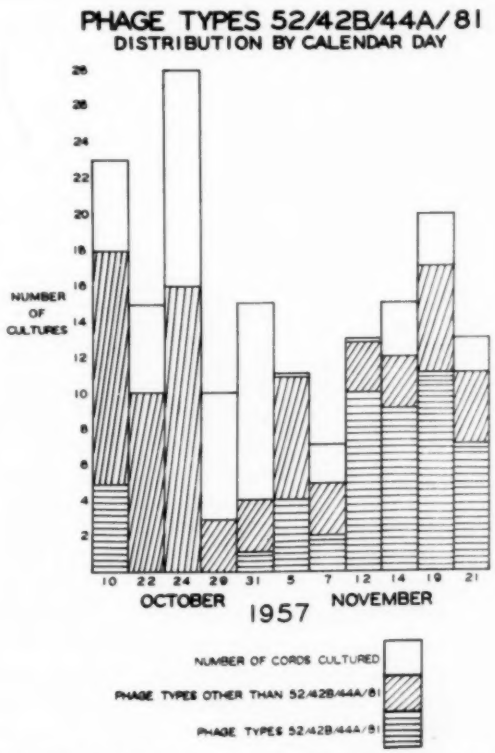

Fig. 3.—The incidence of Phage types 52/42B/44A/81 by calendar day.

As may be seen in Table V, Phage types 52/42B/44A/81 were found in 42 of 144 infants in the nursery. When one of the group 52/42B/44A/81 appeared in the 273 cultures, all of them appeared with but three exceptions. In these three, 42B appeared on one occasion and 44A appeared alone on two occasions, that is, not in combination with the others of this group of four. Thirty per cent, then, of the patients in the newborn nursery had phage types that are generally considered pathogenic, and with over a 90 per cent follow-up at the end of one month there was no increased incidence of

Staphylococcus infection in the infants present in the nursery during this period of 30 per cent carrier rate. The distribution of "pathogenic" phage types on the days cultures were taken indicates a fluctuation from complete absence in one week to a relatively high incidence the following week as seen in Fig. 3.

Two breast abscesses were reported in mothers of this group of infants. The infants of these mothers had the "pathogenic" strain of *Staphylococcus aureus* present in the cord-cutaneous junction during their nursery stay. Phage types 52/42B/44A/81 were found in only three of the 98 follow-up cultures at or near 30 days of life. All of these three had had the same strain in the nursery. Only one of these had a problem with his skin, as reported above.

DISCUSSION

The umbilical stump has been the suspected and real source of serious infection to the individual infant,[4-7] the media for luxuriant growth of a variety of organisms that was of interest to the bacteriologist,[1, 8, 9, 10, 11, 19] a problem in handling for the clinician (from bath to no bath, from dressing to no dressing, from powder to alcohol), and now a serious contributing factor in spread of pyoderma in the newborn nursery.[1, 12, 13, 19] When we first found our Staphylococcus rate as high as it was in the umbilical area we were concerned that we had a contaminated nursery, and therefore, the procedure was carried out in a local civilian hospital. The findings were quite comparable. Although the number of cultures was small, the trend was similar. We did not alter our routine, which closely follows the standards of newborn care as outlined by the American Academy of Pediatrics *Handbook on Standards of Newborn Care*, except that we required the charge nurse of each eight-hour shift to be personally responsible for the cleansing of the cord and cord-cutaneous junction with 70 per cent alcohol at least once on her eight-hour tour. Although at any one time 85 per cent of the cords had Staphylococcus in them, out of 211 patients followed serially during a six-day hospitalization coagulase-positive *Staphylococcus aureus* was found in 210 at least once during their hospitalization. The consistency of an 80+ per cent incidence of recovery of the Staphylococcus from the cord over a 2½-year period serves only as a reminder that proper individual technique is a basic essential in caring for the newborn infant. A high incidence of beta Streptococcus, although not grouped, emphasizes a potential and reminds us of past experiences, such as in Chamberlain's[6] report in 1936 of 15 out of 26 fatal cases of omphalitis where beta hemolytic Streptococcus was implicated. The authors realize that most of the bacteria found during this study are considered normal flora of the skin, whether "transient" or "resident,"[14] but the authors feel that the high incidence is worthy of note. The ease of recovery with a sterile dry applicator without a holding media except that which is obtained coincidentally in the taking of the culture indicates colonization and a constant source of contamination or recontamination of the air and personnel over and above the quantity found on the remainder of the skin.

The findings of the two laboratories were compared during this series as

the weekly cultures were continued during Phase III. The method of obtaining cultures remained the same, and although the cultures were taken by two different individuals at slightly different times, one group taken directly to the laboratory, the other group sent "through channels," the culture reports compared closely between laboratories with the exception that the Research Laboratory consistently identified a greater variety of organisms.

The single most interesting finding was a 30 per cent incidence of phage type 52/42B/44A/81 in the newborn nursery unassociated with an increased incidence of pyoderma either in the nursery or in a 90+ per cent follow-up through the first month of life. With so much recent epidemiological work in nurseries[15-25] following epidemics of pyoderma, the authors feel this information will be of interest to the epidemiologists.

SUMMARY

1. Flora of the umbilical stump are listed according to the frequency of appearance in our nursery as cultured by two separate laboratories.

2. An incidence of 80+ per cent *Staphylococcus aureus,* coagulase positive, was found in the umbilical stump by the fourth day of life over a 2½-year period.

3. Two hundred and ten of 211 infants had *Staphylococcus aureus,* coagulase positive, in the umbilical area on at least one occasion in the first six days of life.

4. Phage types 52/42B/44A/81 were found in 30 per cent (42 of 144) of infants cultured while in the nursery. With over a 90 per cent follow-up, this 30 per cent finding was not associated with an increased incidence of pyoderma.

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Feeding Advice

From the foregoing remarks, we may conclude:

1. That maternal warmth and the semi-erect position are essential to a child while it is taking its food. Hence the need of a particular kind of bottle.

2. That asses' milk does not appear from its composition calculated to do good to a child, if persisted in for any length of time.

3. That goats' milk is proved, from experience, to be even in its normal state most efficacious to a child; and that if the goat be properly dieted, it will yield a milk closely resembling human milk.

4. That as in the case of the goats' milk, so in regard to the cow, if the milk be pure and the animal be properly dieted, the same results obtain in both cases; but that *in towns* cows are so shamefully kept and fed, and the milk is so watered, that cows' milk cannot be considered, as a rule, as wholesome food.

5. That to remedy these abuses, stringent laws are imperatively called for.

6. That artificial milks closely resembling human milk may be readily prepared from pure cows' milk; and that these, together with beef-tea and eggs, may occasionally be safely substituted for breast milk.

From an article on the MORTALITY OF INFANTS IN FOUNDLING INSTITUTIONS. C. H. M. ROUTH. BRITISH MEDICAL JOURNAL, 1858.

RHEUMATIC PNEUMONITIS

Part II. Report on the Clinical and Laboratory Findings in Twenty-three Patients

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DURING the past eight years we have had the opportunity to follow 16 patients with severe rheumatic fever who died, whose autopsy studies revealed characteristic but not specific microscopic changes in the lung parenchyma compatible with the diagnosis of rheumatic pneumonitis in addition to the usually observed changes in rheumatic heart disease. We also selected 7 patients with severe rheumatic fever who survived and who, we felt, had rheumatic pneumonitis because their clinical and laboratory findings were strikingly similar to those of the 16 patients who expired.

Although much has been written on the subject of rheumatic pneumonitis, little has appeared exclusively in the pediatric literature.[1-5] There is skepticism about the existence of this rheumatic manifestation and disagreement about its incidence. We feel that it does occur, is not rare, and can be demonstrated by characteristic but not specific changes in the lung parenchyma. We feel also that it does not always lead to death and may be demonstrated ante mortem, especially in patients with severe rheumatic fever. Although there are many reports on the use of cortisone and ACTH in the treatment of rheumatic fever, there is little mention of the response of rheumatic pneumonitis to these hormones. Our experiences with them may, therefore, be of some interest.

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METHODS

The clinical course of each of the 23 patients was analyzed. Electrocardiograms and serial roentgenograms were studied when available. All patients were treated in essentially the same manner. Twelve patients in Group I (nonsurvivors) and 3 in Group II (survivors) were given aspirin on the basis of 0.14 Gm. per kilogram per day in 4 divided doses. Seven patients in Group I and 5 in Group II were treated with cortisone or Meticorten and one patient was treated with ACTH. The dosage of hormone was variable. All patients received parenteral penicillin and streptomycin. All were digitalized with digitoxin (0.033 mg. per kilogram total dose; maintenance, 10 per cent of total dose per day) and kept in oxygen tents. Morphine sulfate and Mercuhydrin were used when indicated. All patients had initial blood and throat cultures.

TABLE I. CLINICAL AND LABO ATO

NO.	PATIENT	AGE (YR.) AND SEX	RHEUMATIC FEVER STATUS	COUGH	FEVER	TACHY-CARDIA	TACHYP-NEA	EN-LARGED LIVER	EDEMA	CHEST PAIN	
1	T. B. B.	5 F	Initial	0	+	+	+	+	0	0	Poor
2	I. M. S.	10 F	Initial (?)	+	+	+	+	+	+	+	Fair
3	T. S. R.	7 M	Prolonged initial	0	+	+	+	+	0	0	Poor
4	J. W.	10 M	Recurrent	0	+	+	+	0	0	0	Poor
5	S. S. L.	9 F	Prolonged initial	+	+	+	+	+	+	+	Poor
6	K. R. B.	7 M	Prolonged initial	+	+	+	+	0	0	0	Poor
7	C. M. S.	12 M	Prolonged initial	+	+	+	+	+	0	0	Poor
8	T. J. P.	4 M	Prolonged initial	0	+	+	+	+	0	0	Poor
9	R. R. C.	14 M	Recurrent	0	+	+	+	+	0	0	Poor
10	R. P.	5 M	Initial	0	+	+	+	0	0	0	Poor
11	V. M. M.	9 F	Recurrent	+	+	+	+	+	+	+	Nor-m
12	F. A. A.	12 F	Recurrent	+	+	+	+	+	+	+	Poor
13	A. L. K.	3 M	Initial	+	+	+	+	+	0	0	Poor
14	J. L. D.	6 M	Initial	+	+	+	+	0	0	+	Poor
15	S. L. C.	6 F	Initial	+	+	+	+	0	0	+	Poor
16	D. A. H.	14 M	Recurrent	0		+	+	+	+	0	Poor

*Murmurs = (a) systolic apical blow transmitted to axilla, or (b) systolic and diastolic blow at apex transmitted to axilla, or (c) systolic and diastolic blow at right base.
†Hemoglobin, less than 9 Gm.
‡White blood cells 12,000 or more.

Sixteen patients (Group I) died. The gross and microscopic examinations were performed by the Washington University Department of Pathology, and the diagnosis of rheumatic fever was established. Aschoff bodies or typical verrucae were found in the hearts. Selected blocks of lung were recut and stained with phosphotungstic acid-hematoxylin, aldehyde fuchsin Von Giesen-hematoxylin, Masson's trichrome, and periodic acid-Schiff stains. Microsections of the lungs were examined especially for fibrinous exudate in alveolar sacs or respiratory ducts, hyaline membrane, necrosis of alveolar walls and thrombi. Pathologic changes were graded as "slight" if less than 10 per cent of the tissue available for microscopic study was estimated to be involved, "moderate" for 10 to 20 per cent, and "advanced" for over 20 per cent involvement.[6] Seven patients (Group II) survived a very severe form of rheumatic fever, and it was felt that

FINDINGS IN PATIENTS WHO DIED

	HEART		BLOOD		ECG				X-RAY		THERAPY	
TONES	MURMUR*	HYPERTROPHY	ANEMIA†	LEUKOCYTOSIS‡	PROLONGED A-V TIME	MYOCARDIAL DISEASE	LEFT VENT. HYPERTROPHY	OTHER	HEART ENLARGEMENT	PULMONARY INFILTRATION	ASA	HORMONES
Poor	0	0	+	+	0	+	0	0	+	+	0	0
Fair	+	+	+	+	0	+	0	0	+	+	+	0
Poor	+	+	0	0	+	+	0	0	–	–	+	0
Poor	+	+	0	+	+	0	0	0	+	+	+	0
Poor	+	+	+	+	+	+	0	0	–	–	+	+ ACTH
Poor	+	+	+	+	0	+	0	0	+	+	+	+
Poor	+	+	0	+	+	0	0	Pericarditis‖	+	0	0	0
Poor	+	+	+	0	–	–	–	–	+	+	+	+
Poor	+	+	+	+	+	0	+	V.P.C.¶	+	+	+	0
Poor	0	0	0	+	+	0	0	0	–	–	+	+
Normal	+	+	0	+	0	+	+	0	+	+	0	0
Poor	+	+	0	+	+	0	0	0	–	–	+	0
Poor	+	+	+	+	0	+ (Dig.)§	0	0	0	+	+	+
Poor	+	0	+	+	0	0	0	0	+	+	+	+
Poor	+	0	+	+	0	0	0	0	+	+	+	+
Poor	+	+	0	+	+	+		0	+	0	0	0

§Changes may have been due to digitoxin.
‖Findings were compatible with pericarditis.
¶Ventricular premature contraction.

they had rheumatic pneumonitis. Proof of this was impossible during life, but the clinical and laboratory findings and especially the radiologic changes were strikingly similar to those of the 16 patients who died; therefore, we felt the diagnosis of rheumatic pneumonitis was justified.

RESULTS

Nonsurvivors (Group I).—

Clinical and laboratory findings: The important clinical and laboratory findings of the patients who died (Group I) are summarized in Table I. Rheumatic pneumonitis developed in 5 patients with their initial attack of rheumatic fever; i.e., by history these patients were ill less than one month at the onset of the pneumonitis. Five patients were ill with rheumatic fever for one month or more when they developed rheumatic pneumonia. Of the remaining six patients, each had one or more previous episodes of rheumatic fever before this final illness.

There was no evidence that this rheumatic manifestation showed any predilection for either the initial episode or recurrent episodes of rheumatic fever. Nine patients showed definite anemia (hemoglobin, <9 Gm. per 100 ml.) and 15 showed leukocytosis (>12,000 white blood cells). All but one patient had fever, and this patient, D. A. H., was admitted in a moribund state and expired in less than 24 hours. Nine patients had coughs; only 6 complained of chest pain. The most striking, consistent findings were the extreme tachypnea and dyspnea, although cyanosis was minimal. Upon examination of the lungs, the physical findings were quite variable, but careful examination was difficult because of the critical status of the patient. Evidence of patchy consolidation and scattered râles was encountered frequently. These abnormal findings frequently changed from day to day and were migratory. In some patients the physical findings were surprisingly minimal, although the roentgenograms and autopsy studies revealed extensive involvement. All patients had tachycardia. The heart tones were of poor quality in all except one patient, and all except 2 had systolic apical murmurs transmitted to the axilla. In half of the patients there was an associated diastolic murmur. Electrocardiograms were available for analysis in 14 patients. The significant changes were either prolonged atrioventricular conduction time, evidence of myocardial disease (before digitoxin was started), and left ventricular enlargement. In 2 patients the electrocardiograms were within normal limits.

Radiographic findings: Chest roentgenograms were obtained in 12 of the 16 patients of Group I. All but one revealed definite cardiac enlargement. The enlargement was usually generalized and of a marked degree.

Only 10 of the 12 patients demonstrated roentgenographic evidence of pneumonia. One of the 2 patients, without roentgenographic evidence of pneumonia (C. M. S.), died the day following his last examination, and pathologic examination confirmed the presence of rheumatic pneumonia. No explanation for the lack of roentgenographic findings was apparent. The other patient did not have roentgenographic examinations within the terminal period.

Of the 10 patients with roentgenographic evidence of pneumonia, 7 exhibited diffuse, homogeneous zonal infiltrates variously occupying the inner, middle, and outer thirds of the lung fields. This infiltrate was usually bilateral and was characterized by a clear zone about the hila. The appearance was similar to that seen in so-called "azotemic pneumonia" or "acute pulmonary edema."

Two patients demonstrated segmental or lobar infiltrates suggesting organization or infarction. One patient appeared to present both types of infiltrates.

Although subsequent pathologic examination of the specimens revealed instances of these distinct types of infiltrates, the correlation with the roentgenographic findings was poor.

Pathologic findings: Table II gives the pertinent microscopic findings in the lungs of the patients in Group I. The microsections of the lungs were examined and graded as to extent of involvement of the lung parenchyma by the pathologic process. As will be

TABLE II. PATHOLOGIC FINDINGS IN PATIENTS WHO DIED*

NO.	PATIENT	AGE (YR.)	SEX	RACE	FIBRIN	HEMOSIDERIN	HYALINE MEMBRANE	INFARCT	EDEMA	ORGANIZATION	SEVERITY	BACTERIAL PNEUMONIA
1	T. B. B.	5	F	W	A	A	S	0	S	S	M	0
2	I. M. S.	10	F	W	S	M	M	0	M	0	M	0
3	T. S. R.	7	M	W	M	0	0	0	0	S	S	0
4	J. W.	10	M	W	M	0	M	0	M	S	M	+
5	S. S. L.	9	F	W	A	0	M	0	S	A	M	0
6	K. R. B.	7	M	W	S	S	S	0	M	0	M	0
7	C. M. S.	12	M	C	M	S	M	0	M	S	M	+
8	T. S. P.	4	M	W	S	0	0	0	0	0	S	+
9	R. R. C.	14	M	W	S	M	0	0	S	0	S	0
10	R. P.	5	M	W	S	S	M	0	A	0	M	+
11	V. M. M.	9	F	C	S	M	0	0	0	S	S	0
12	F. A. A.	12	F	W	M	M	0	0	M	M	M	+
13	A. L. K.	3	M	W	M	S	0	0	M	S	M	+
14	J. L. D.	6	M	W	M	M	M	0	A	S	M	0
15	S. L. C.	6	F	W	M	A	0	0	S	A	M	+
16	D. A. H.	14	M	W	S	S	0	0	M	0	S	0

S = Slight, less than 10 per cent of the tissue available for microscopic study was estimated to be involved.

M = Moderate, 10 to 20 per cent of the tissue available for microscopic study was estimated to be involved.

A = Advanced, over 20 per cent of the tissue available for microscopic study was estimated to be involved.

Severity = Edema + Fibrin + Organization + Hyaline membrane.

*Table prepared by F. R. Scott, W. A. Thomas, and J. M. Kissane, of the Department of Pathology, Washington University School of Medicine.

noted, fibrin deposition in the alveoli was found in all patients; hemosiderin deposits were found in 12 patients; 8 had hyaline membrane formation; 13 showed evidence of pulmonary edema; and 10 showed organization of varying degree in the microsections examined. Infarction was not encountered in any patient. The over-all extent of involvement was then graded on the basis of the finding of edema, fibrin, organization, and hyaline membrane. It will be noted that 11 of the 16 patients have 10 to 20 per cent involvement by rheumatic pneumonitis of the lung tissue examined. The presence of bacterial pneumonia was recognized in 7 patients, but the involvement was minimal, and it was felt that this was not an important contributing cause of death.

Survivors (Group II).—

Clinical and laboratory findings: Table III is constructed in the same manner as Table I and is a summary of the important clinical and laboratory findings in the 7 patients (Group II) who survived an attack of rheumatic pneumonitis. As will be noted, 2 of the patients each had had one or more previous attacks of rheumatic fever; 3 patients were ill for one month or more before they developed rheumatic pneumonitis; and 2 were ill for less than one month prior to this complication. The other findings are quite similar to those in the patients of Group I.

Radiographic findings: Numerous chest roentgenograms were available for all the patients of Group II. Six of the 7 had generalized cardiac enlargement. In most of these patients the heart appeared to enlarge during the pneumonic phase and the size decreased only slightly as they improved. All 7 patients exhibited pneumonia by roentgenographic

TABLE III. CLINICAL AND LABORATORY FINDINGS

NO.	PATIENT	AGE (YR.) SEX	RHEUMATIC FEVER STATUS	COUGH	FEVER	TACHY-CARDIA	TACHYP-NEA	ENLARGED LIVER	EDEMA	CHEST PAIN	TOXES
1	E. A. R.	9 M	Recurrent	0	+	+	+	+	0	+	Poor
2	M. F. M.	12 F	Prolonged initial	0	+	+	+	0	0	+	Poor
3	B. B. H.	5 M	Prolonged initial	+	0	+	+	+	0	0	Poor
4	O. S. E.	6 F	Recurrent	0	+	+	+	0	0	+	Poor
5	J. R. K.	6 M	Initial	+	+	+	+	+	0	0	Poor
6	A. L. F.	12 F	Prolonged initial	0	+	+	+	+	0	0	Poor
7	M. S.	6 M	Initial	+	+	+	+	+	?+	?+	Poor

*Murmurs = (a) systolic apical blow transmitted to axilla, or (b) systolic and diastolic blow at apex transmitted to axilla, or (c) systolic and diastolic blow at right base.

†He
‡Wh
§Ve

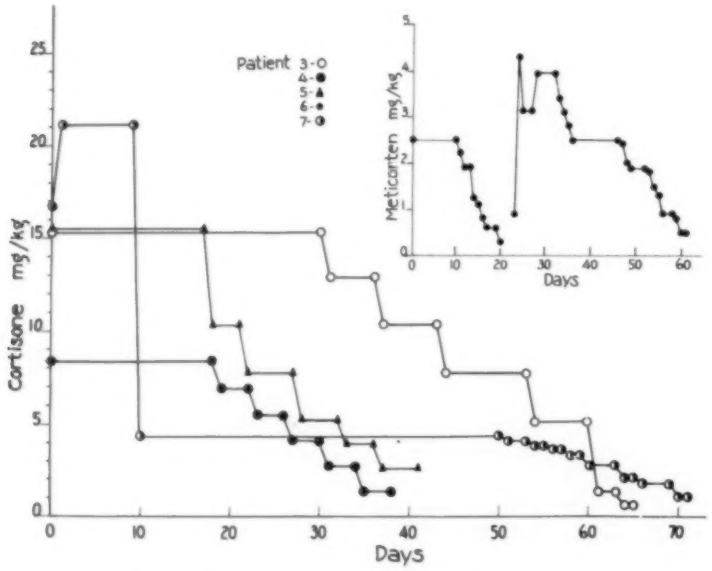


Fig. 1.—Hormone dosage in survivors.

examination and, of these, 4 were zonal, 1 was segmental, and 2 demonstrated combinations of the two types. All cleared completely over periods of 1 to 4 weeks.

THERAPY

Treatment of patients with rheumatic pneumonitis was disappointing, for all survivors had evidence of residual heart disease at the end of 1 to

FINDINGS IN PATIENTS WHO SURVIVED

	HEART		BLOOD		ECG				X-RAY		THERAPY	
TONES	MURMUR*	HYPERTROPHY	ANEMIA†	LEUKOCYTOSIS‡	PROLONGED A-V TIME	MYOCARDIAL DISEASE	LEFT VENT. HYPERTROPHY	OTHER	HEART ENLARGEMENT	PULMONARY INFILTRATION	ASA	HORMONES
Poor	+	+	0	+	+	+	0	0	+	+	+	−
Poor	+	+	0	0	0	0	0	VPC§	+	+	+	−
Poor	+	0	+	0	0	0	0	0	0	+	0	+
Poor	+	+	+	+	+	0	+	0	+	+	0	+
Poor	+	+	0	+	+	+	0	0	+	+	0	+
Poor	+	+	0	+	0	+	0	0	+	+	0	+
Poor	+	+	+	+	+	+	0	VPC	+	+	+	+

†Hemoglobin, less than 9 Gm.
‡White blood cells, 12,000 or more.
§Ventricular premature contractions.

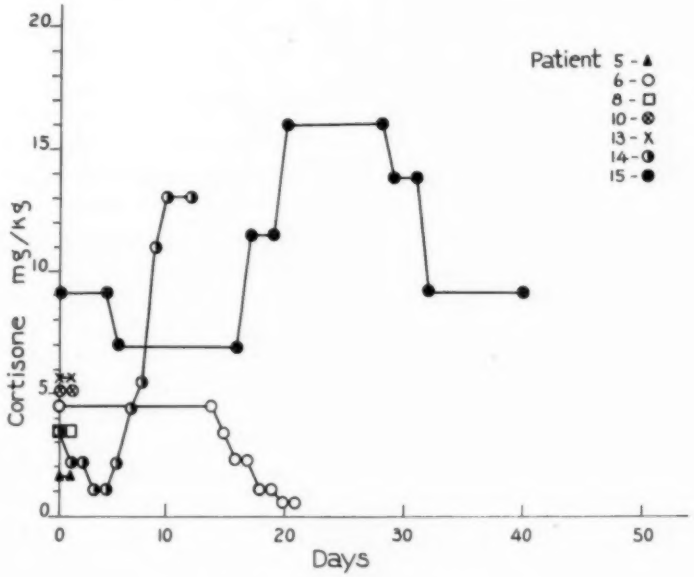


Fig. 2.—Cortisone dosage in nonsurvivors.

3 years of follow-up. Our experience definitely indicates that the development of rheumatic pneumonitis in the course of active rheumatic fever is a grave prognostic manifestation.

Six of the 7 survivors had obvious cardiomegaly as demonstrated on roentgenograms of the chest and all had auscultatory findings compatible with mitral insufficiency. Five of the

7 survivors, who were treated with cortisone, had residual mitral insufficiency and cardiomegaly, and 2 also had aortic insufficiency. The 2 patients who were not treated with hormone had evidence of mitral and aortic insufficiency as well as marked cardiomegaly. This suggests that hormone therapy seems to decrease the severity of the residual heart disease, but the number of patients is so small that such a conclusion is not entirely justified.

It is also difficult to evaluate hormone therapy in terms of its effect on the survival of patients with rheumatic pneumonitis. Briefly stated, our results are as follows: Nine patients did not receive hormone and 2 survived. Twelve patients were treated with hormone and 5 survived. In Figs. 1 and 2 are summarized the data on patients treated with hormone. The patients are divided into survivor and nonsurvivor groups. It is apparent that the dosage is not uniform. These patients were collected over a 5-year period, and the treatment schedules varied with the recommended dosage at that time. In the survivor group the dosage of hormone was much more liberal since these patients were in the hospital during the past two years and reflect the trend toward higher hormone dosage. We were guided by the course of the individual patient and did not attempt to set up a rigid program that might have jeopardized the patient's welfare, and, therefore, the length of treatment was somewhat variable. The number of patients in this entire series is, of course, too small, and the schedule of treatment with hormone too variable, to warrant an accurate evaluation of hormone therapy; but the suggestion is warranted that hormone therapy may increase the chance of survival in the child with rheumatic pneumonitis and may possibly decrease the severity of the residual heart disease in those who survive.

CASE SUMMARIES

Four patients have been selected to illustrate the clinical course of rheumatic pneumonitis. Two of the patients were treated with hormone. The first patient did not receive hormone and died after a short fulminating course. The second patient was treated with hormone, but also died after an illness of 2 months and demonstrated, in contrast, the long course rheumatic pneumonitis may take. The third patient received Meticorten and recovered after a prolonged illness, but was left with cardiomegaly and mitral insufficiency. The fourth patient did not receive hormone and also survived after a prolonged illness and was left with cardiomegaly and mitral and aortic insufficiency. Proof of the diagnosis in the two patients who survived was not positive. It was felt, however, that the clinical and laboratory findings were sufficiently similar to those of the patients who died to justify the diagnosis of rheumatic pneumonitis.

CASE 1.—I. M. S. This patient's course was short and fulminating and she expired 14 days after hospital admittance. Her hospital course is depicted in Fig. 3. The most striking feature is her respiratory rate, which at times rose to 80 per minute. Figs. 4 and 5 represent roentgenograms of the chest taken, respectively, 2 and 12 days after admittance. The early perihilar, zonal infiltrate progressed rather rapidly and became most marked on the right where it involved

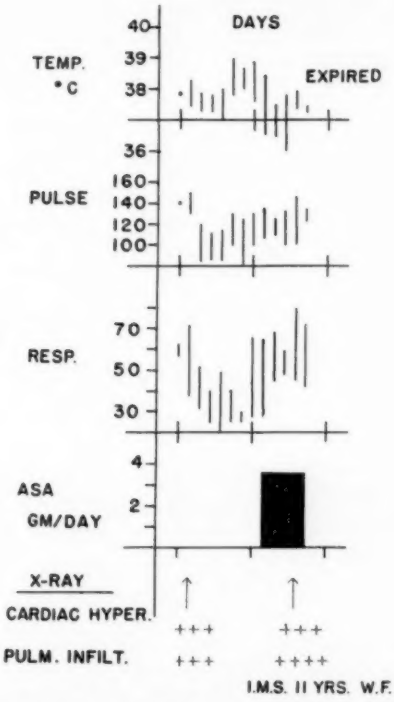


Fig. 3.—Rheumatic pneumonia. Course of Patient I. M. S.

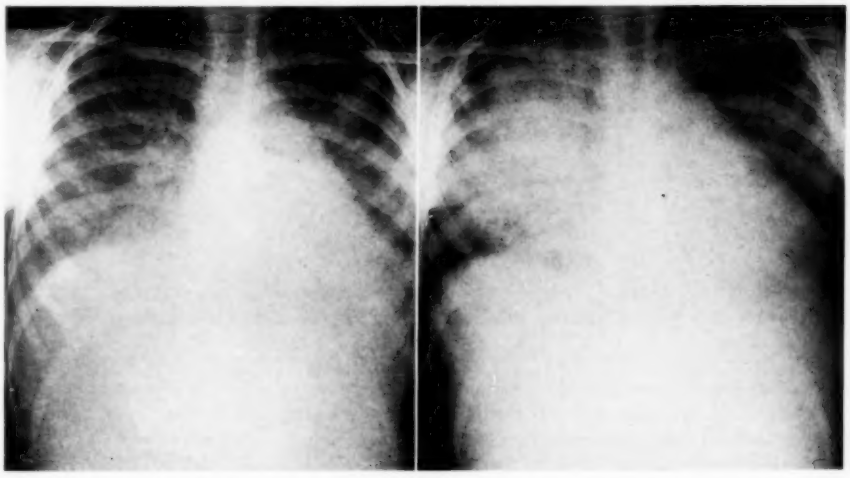


Fig. 4. Fig. 5.

Fig. 4.—Patient I. M. S. Roentgenogram taken two days after admittance. There is bilateral zonal infiltration involving both lower lungs, and the heart is enlarged.

Fig. 5.—Patient I. M. S. Roentgenogram taken 2 days before death reveals more extensive involvement on the right side and progressive cardiac enlargement.

the inner and middle thirds of the lung. Progressive cardiac enlargement was also noted. The findings at autopsy were:

1. Severe rheumatic myocarditis with hypertrophy and dilatation of the heart (240 grams).
2. Serofibrinous pericarditis (160 c.c.) and bilateral serofibrinous pleurisy.
3. Verrucous endocarditis of the mitral and aortic valves.
4. Fibrous thickening of the mitral valve with moderate shortening of the leaflets.
5. Fibrous thickening of the endocardium of the left atrium.
6. Rheumatic pneumonitis involving all lobes of the lungs.

there is a thick fibrinous material closely packed against the alveolar wall. The inflammatory cells are primarily mononuclears.

CASE 2.—S. C. This patient, in contrast to the above, illustrates the chronic course rheumatic pneumonitis may take and also represents a failure of hormone therapy, since she died after an illness of over two months. She had an initial febrile period (Fig. 7) and a persistent tachycardia throughout her course. The most striking feature was the marked tachypnea. Serial roentgenograms demonstrate the relentless course of the disease. Ten days after admittance the

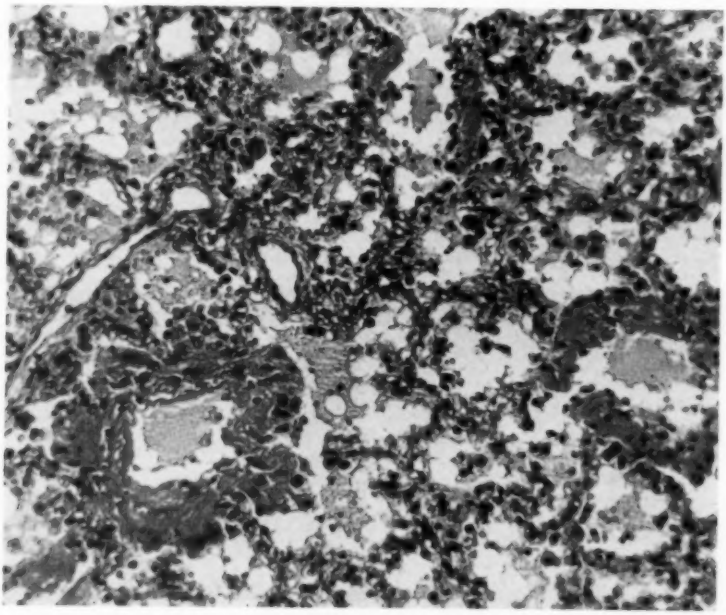


Fig. 6.—Microsection of lung of Patient I. M. S., showing edema and congestion. Some alveolar spaces are filled with edema fluid. In other areas, the alveoli show fibrinous material packed against the alveolar walls. The inflammatory cells are primarily mononuclears.

Fig. 6 is a photograph of a microsection of the lungs which reveals edema and congestion. Some alveolar spaces are filled with a very thin substance—edema fluid. In other areas

chest roentgenogram (Fig. 8) revealed cardiomegaly but no evidence of infiltration. Six days later (Fig. 9) examination demonstrated a moderately extensive pneumonia, most

marked in the right upper lung field. Thirty-two days after admittance (Fig. 10) the chest examination more clearly showed the zonal character of the pulmonary infiltrate occupying the outer third of the right lung and maintaining a clear zone in the perihilar area. Pneumonia appeared to have decreased in the left lung, but progressive cardiac enlargement was apparent. Twelve days later, 3 days before death (Fig. 11), the pneumonia on the right had decreased, an infiltrate had reappeared on the left, and the heart had continued to enlarge. The findings at autopsy were:

1. Rheumatic pancarditis with rare Aschoff bodies.
2. Hypertrophy and dilatation of the heart (180 grams).
3. Hydropericardium (50 c.c.).
4. Both lungs were a mottled, dark red-brown with the lobular architecture somewhat indistinct. There was advanced organizing pneumonitis of all lobes of the lungs.

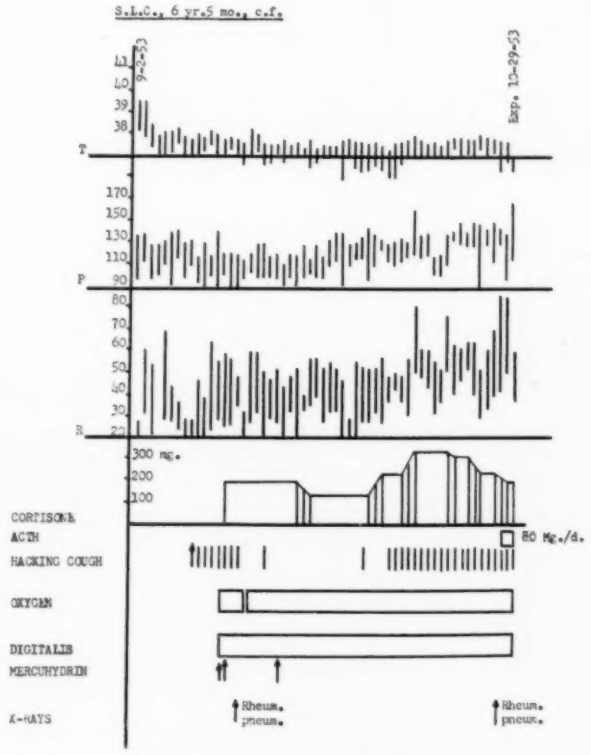


Fig. 7.—Hospital course of Patient S. C.

A microsection of the involved lung tissue (Fig. 12) revealed many of the alveolar spaces filled with fibroblasts so that the alveolar walls were difficult to identify. There were also areas of hemorrhage, edema, and mononuclear cell infiltration. It is interesting to speculate on the relatively few findings typical of severe rheumatic fever in the microsections of the heart. This

Fig. 8.

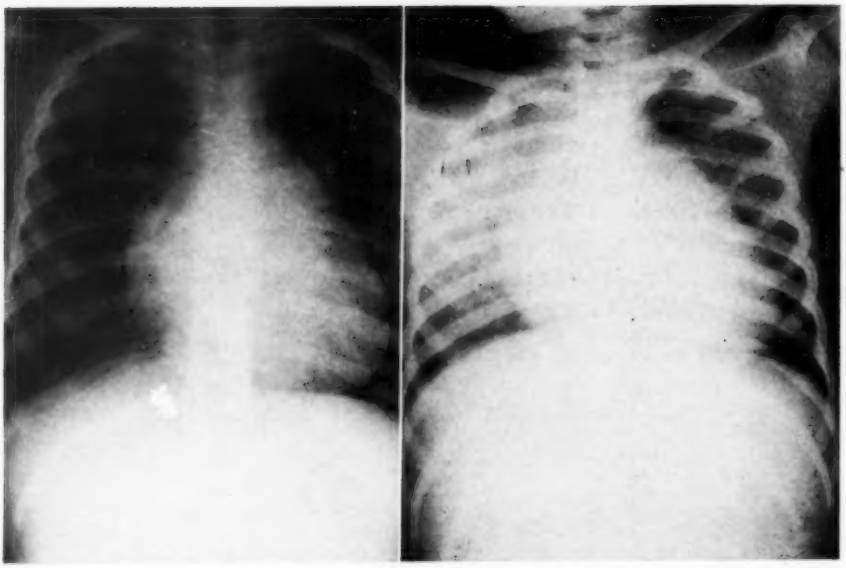


Fig. 9.

Fig. 8.—Patient S. C. Roentgenogram taken 10 days after admittance reveals cardiomegaly but no evidence of infiltration.

Fig. 9.—Patient S. C. Roentgenogram taken eighteen days after hospital admittance demonstrates infiltration involving the entire right lung and a portion of the left upper lung. The heart appears larger.

Fig. 10.

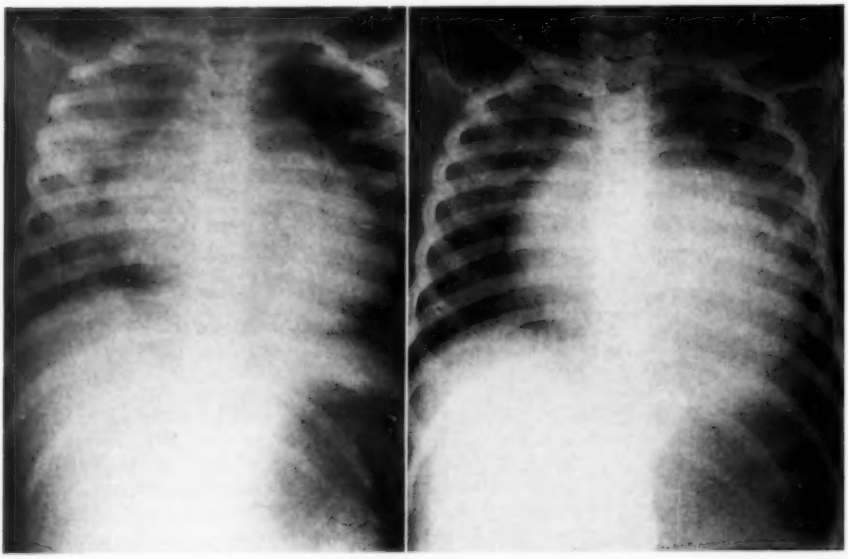


Fig. 11.

Fig. 10.—Patient S. C. Roentgenogram taken 32 days after admittance clearly demonstrates the zonal character of the infiltrate involving the outer third of the right lung. A "clear space" can be seen in the perihilar area. Pneumonia has practically disappeared on the left but the heart continues to enlarge.

Fig. 11.—Patient S. C. Roentgenogram taken 3 days before death reveals some clearing of the infiltrative process on the right but more definite involvement on the left. The heart size has again increased.

may possibly be related to the prolonged course of hormone therapy.

CASE 3.—M. S. The course of this patient who survived will illustrate the clinical and radiologic features which justify the diagnosis of rheumatic pneumonia. The course of this patient (Fig. 13) is quite similar to that of Patient S. C. previously described. Here, again, we note, as in Patient S. C., the fever, tachycardia, and marked tachypnea. Patient M. S. did have more dyspnea than S. C. Patient M. S., who was 1 year younger, but at about the same level of physical development as S. C., received more hormone per kilogram of body weight per day. Although he survived, he was left with residual cardiomegaly of moderate degree and mitral insufficiency. A number of chest roentgenograms were taken during his illness, demonstrating a variable pattern of pulmonary infiltration extending over a period of two months. Upon admittance, a chest roentgenogram (Fig. 14) revealed marked cardiomegaly and extensive pneumonia. The pulmonic infiltrate on the right appeared segmental, suggesting pulmonary infarction or organizing pneumonia, while the infiltrate on the left was more zonal in character. Nineteen days later (Fig. 15) the pneumonia became more diffuse and occupied the inner and middle zones of both lungs. Only 4 days later (Fig. 16) examination demonstrated marked improvement of the pneumonia; and finally, 2 months after admittance, the chest roentgenogram (Fig. 17) revealed complete clearing of the pulmonary infiltrate. Marked cardiac enlargement and chronic pulmonary congestion persisted.

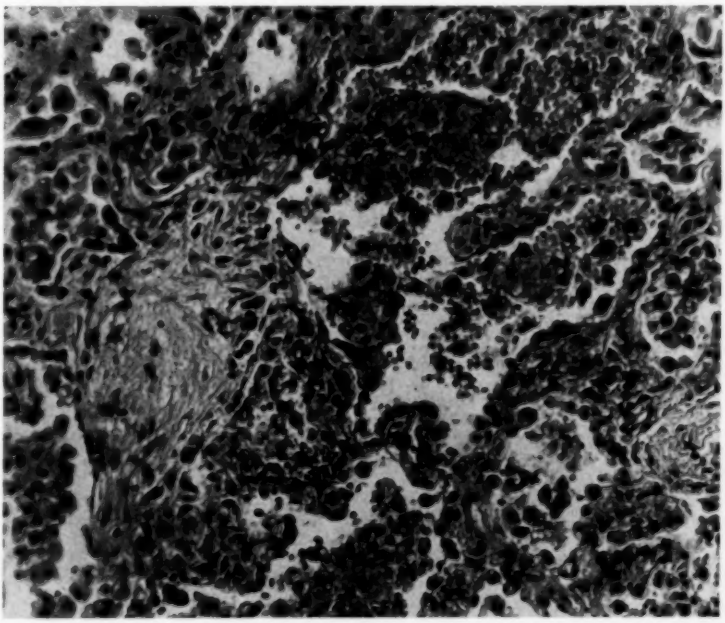


Fig. 12.—Microsection of lung of Patient S. C. Many alveolar spaces are filled with fibroblasts so that the alveolar walls are difficult to identify. There are also areas of hemorrhage, edema, and mononuclear cell infiltration.

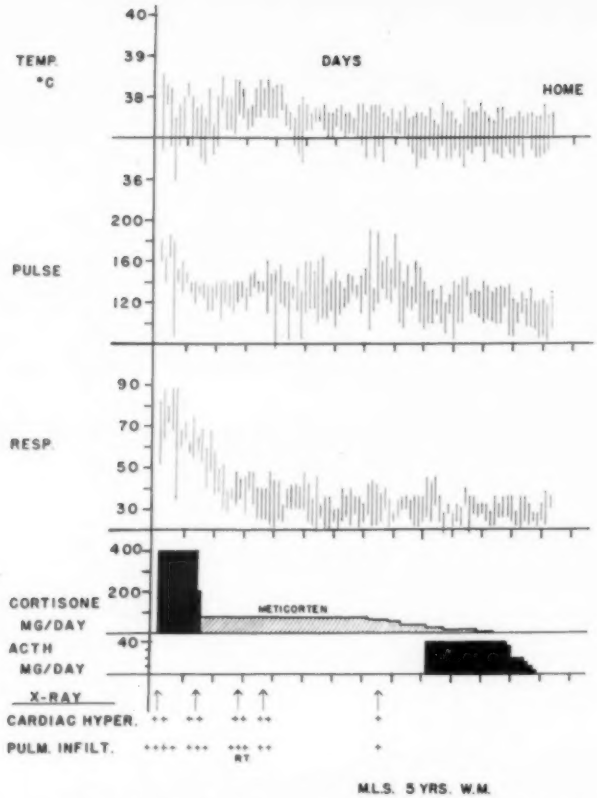
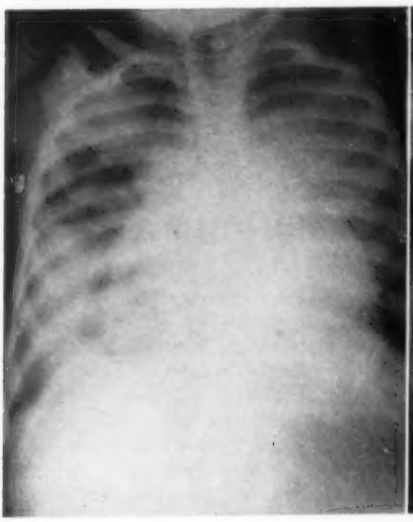


Fig. 13.—Rheumatic pneumonia. Hospital course of Patient M. S.

Fig. 14.



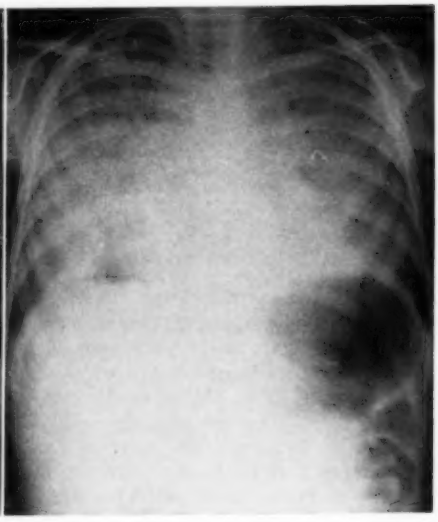


Fig. 15.

Fig. 14.—Patient M. S. Roentgenogram made on admittance reveals marked cardiomegaly and extensive pneumonia. Pulmonary infiltrate is segmental on the right and zonal on the left.

Fig. 15.—Patient M. S. Chest roentgenogram made 10 days after admittance reveals persistance of extensive infiltration which has become zonal bilaterally. The heart has increased in size.

Fig. 16.

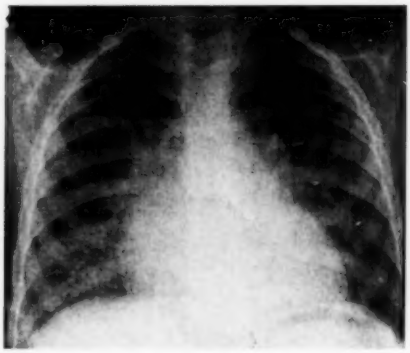


Fig. 17.

Fig. 16.—Patient M. S. Chest roentgenogram made 23 days after admittance shows marked resolution of infiltrative process, but persistance of the cardiomegaly.

Fig. 17.—Patient M. S. Chest roentgenogram made 2 months after admittance demonstrates residual cardiomegaly and pulmonary congestion but no pneumonia.

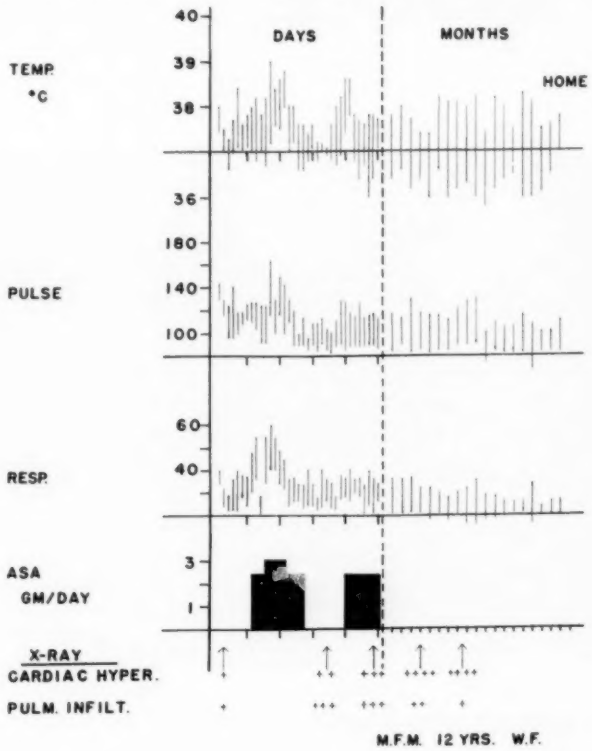


Fig. 18.—Rheumatic pneumonia. Hospital course of Patient M. M.

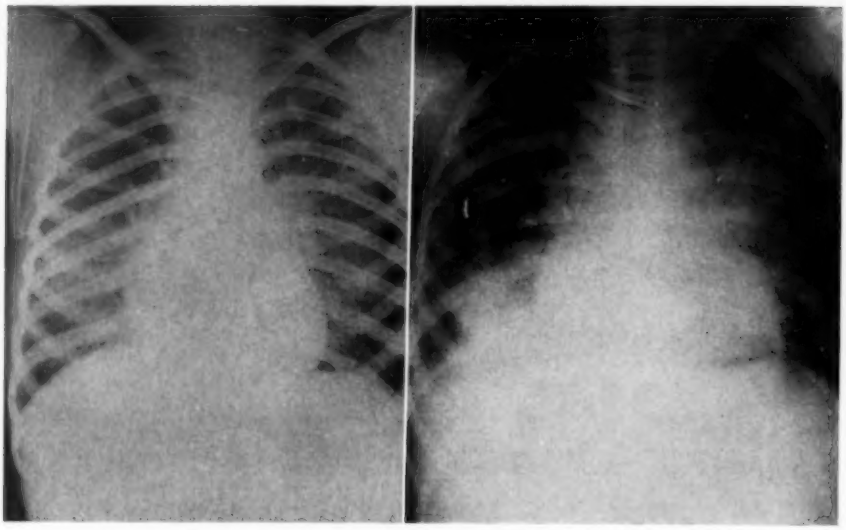


Fig. 19. Fig. 20.

Fig. 19.—Patient M. M. An initial chest roentgenogram taken upon admittance reveals a moderate degree of cardiomegaly and a minimal, bilateral, perihilar infiltration.

Fig. 20.—Patient M. M. Chest roentgenogram made 3 weeks after admittance reveals an interval increase in heart size and a segmental infiltration primarily involving the lower lobes.

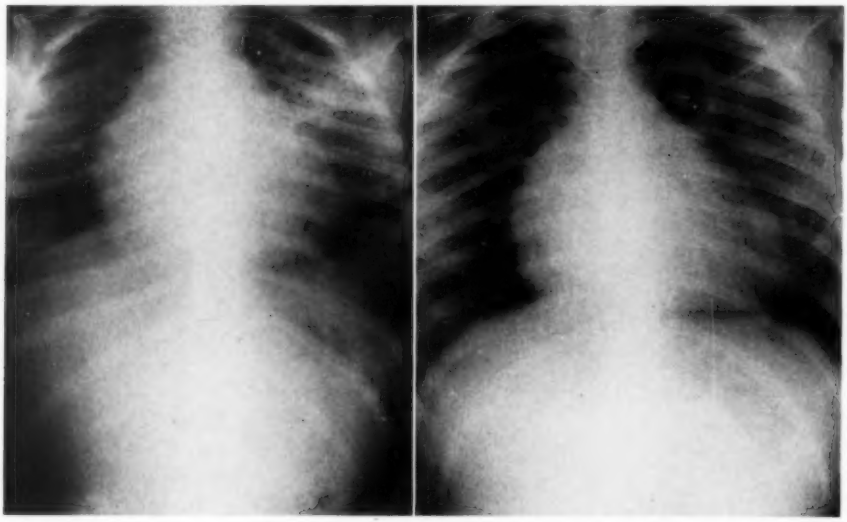


Fig. 21. Fig. 22.

Fig. 21.—Patient M. M. Chest roentgenogram one month after admittance reveals resolution of the lower lobe infiltrate but persistance of minimal pneumonia in both upper lobes. The heart continues to increase in size.

Fig. 22.—Patient M. M. Chest roentgenogram 2 months after admittance reveals clearing of the infiltration and a further increase in heart size.

CASE 4.—M. M. Before the advent of hormone therapy, 2 patients (E. R., M. M.) survived an attack of acute rheumatic fever with associated rheumatic pneumonitis. The course of Patient M. M. will be used to demonstrate the salient features which justify the diagnosis of rheumatic pneumonitis in the living patient and, also, that survival was possible without hormone therapy. This patient was in the hospital for 3 months (Fig. 18). She received aspirin during the first month and was in an oxygen tent for 2 months. She was febrile for almost her entire course. Initially, she had marked tachycardia and tachypnea which slowly subsided over the 3-month period. The roentgenogram of the chest upon admittance (Fig. 19) revealed moderate cardiomegaly and a faint, homogeneous zonal infiltrate involving the perihilar zones of both lungs. Three weeks later a chest roentgenogram (Fig. 20) revealed a changing pumonary infiltrate which had become segmental in character and primarily involved the lower lobes. The heart increased in size. One month after admittance (Fig. 21) there was a further increase in cardiac size, but the pulmonary infiltrate was clearing, with bilateral upper lobe infiltrates of moderate extent persisting. One month later, two months after admittance (Fig. 22), the lungs were clear, but marked cardiomegaly persisted. This patient survived, but was left with residual mitral and aortic insufficiency.

DISCUSSION

We feel that attention should be focused upon the subject of rheumatic pneumonitis to emphasize that this rheumatic manifestation does occur in children and may be suspected ante mortem and definitely recognized post mortem. Rheumatic pneumonia is not rare in our experience, since we have collected 23 cases in the last 8 years; and, as will be shown in a subsequent publication, evidence of rheumatic pneumonitis was found in 62 per cent of 87 children who died from rheumatic fever at the St. Louis Children's Hospital between the years 1919 and 1954.[6]

Although much has been written upon the subject, there is relatively little reference to rheumatic pneumonitis exclusively in the pediatric literature. It may be that this manifestation is not recognized as a reaction of the pulmonary vasculature to injury by rheumatic fever, but considered as a secondary reaction to profound myocarditis, congestive failure, or pulmonary edema.

It is important not to confuse rheumatic pneumonitis with bacterial pneumonitis or the more remote possibility of viral pneumonitis, so that therapy is not directed too strongly in those directions. Bacterial pneumonia was not a very likely possibility in the 23 patients of this group. All patients received parenteral penicillin and streptomycin for the greater portion of their illnesses. Those patients who received hormone were usually placed upon Aehromycin also. The zonal distribution and migrating character of the pneumonia by roentgenographic examination made bacterial pneumonia unlikely. Finally, at autopsy, evidence of bacterial pneumonitis was found in 7 of the 16 patients, but the involvement was quite minimal and was felt to be noncontributory to death.

Viral pneumonitis was, of course, not absolutely ruled out in the patients who survived, but, in the patients who succumbed, the pathologic picture in the lungs did not support this possibility in any of the patients. At best, viral pneumonitis, although not absolutely excluded, would be a remote possibility.

The changeable character of the roentgenographic appearance of the lungs as illustrated in the cases presented would make it unlikely that the lung involvement was secondary to congestive failure, to profound myocarditis, or to pulmonary edema, although the infiltrate upon spot examination cannot be distinguished radiographically from acute pulmonary edema. In the microsections of the lungs of the patients who died, it was, of course, easy to distinguish the pathologic picture of rheumatic pneumonitis from the changes caused by congestive failure or pulmonary edema. These three entities—congestive failure, severe myocarditis, and pulmonary edema—may be present concomitantly with the rheumatic pneumonitis; and, in the initial period of illness, it may be impossible to distinguish them from rheumatic pneumonitis. This, however, is not important, since the initial therapeutic approach would not be essentially different even with associated rheumatic pneumonitis. Later in the disease the persistence of the roentgenologic changes in the lungs should alert one to the presence of rheumatic pneumonitis. Since evidence of rheumatic pneumonitis was found in the majority of the rheumatic children who died, one should suspect rheumatic lung involvement, especially in any child desperately ill with rheumatic fever.

The presence of rheumatic pneumonitis should certainly be considered a grave prognostic development in the course of rheumatic fever and is a definite threat to survival. In those patients who do survive and whose pneumonitis clears, there is a severe degree of residual heart disease. This is not surprising, because during the illness there is striking evidence of severe cardiac disease as found by auscultatory, roentgenographic, and electrocardiographic studies. We recognize the possibility that there may be mild forms of rheumatic pneumonitis and conceivably the lungs may be minimally involved, so that survival is possible. In our experience, this has not been encountered, and we regard rheumatic pneumonitis as an indication for continued vigorous therapy until there is evidence of quiescence of the disease in the lungs as well as in the heart.

The evaluation of therapy in this group of patients is difficult. Although the patients are reported as a group, the natural course of the disease was quite different for each patient. This, of course, is true for the milder forms of rheumatic fever and has been one of the reasons for divergent views about effectiveness of hormone therapy. A truly controlled series would mean selecting patients who will have comparable natural courses of rheumatic fever, and this, obviously, is not possible.

Since this group of patients had very severe rheumatic fever, one has to evaluate the therapy as it affected the survival rate of the patients. There is the suggestion that hormone therapy might have been responsible for survival in some of the patients. There is also an impression that the severity of the residual heart disease was less in some of the survivors who received hormone. However, one cannot look upon hormone therapy as dramatically efficacious in the severe form of rheumatic fever. In view of our experience and the experiences of others,[7]

the role of hormone therapy in rheumatic fever is still unsettled and it is because of this that we feel that hormone therapy should not be withheld in the severe forms of rheumatic fever.

CONCLUSIONS

1. There are relatively few studies upon rheumatic pneumonitis in the pediatric literature.

2. Twenty-three patients with rheumatic pneumonitis are presented in this study. Sixteen patients died and the diagnosis was verified by autopsy. Seven patients survived, and evidence is presented to show that this rheumatic manifestation can be diagnosed during life. The 23 patients were accumulated during the past 8 years.

3. Rheumatic pneumonitis is associated with the severe form of rheumatic fever and is a grave prognostic development. This rheumatic manifestation is a serious threat to survival, and those who survive are left with severe residual heart disease.

4. There is the suggestion that hormone therapy may improve the chance of survival and possibly reduce the severity of the residual heart disease in the survivors. Although its efficacy is disappointing, we feel that hormone should be included in the treatment of any child with severe rheumatic fever.

We would like to thank Dr. Alexis F. Hartmann, Sr., and Dr. Park J. White for their help in preparing this manuscript.

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RIGHT HEART CATHETERIZATION IN INFANTS AND CHILDREN

Analysis of Data Obtained in the Study of 218 Patients

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RIGHT heart catheterization has now become an integral part of the evaluation of congenital heart disease in the pediatric age group. From July, 1955, to March, 1957, this procedure was performed in 218 infants and children at the Medical Center of the University of California at Los Angeles. The purpose of this report is to emphasize the ease with which cardiac catheterization can now be performed in this age group, the high degree of accuracy of the results obtained, and the relatively low mortality rate.

MATERIALS AND METHODS

The patients ranged in age from 1 day to 15 years. All were hospitalized and observed for a minimum of two days prior to the catheterization study. Preoperative preparation usually consisted of penicillin prophylaxis and premedication with atropine and Demerol. Thiamylal sodium* was administered rectally in a dosage sufficient to maintain a basal state of anesthesia (33 mg. per kilogram). The catheterization was performed under fluoroscopic control using a Westinghouse image amplifier, with lead screening strategically positioned in order to offer the maximum protection to the operating personnel (Fig. 1).

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*Surital, Parke, Davis & Co.

Nylon ureteral catheters with a single lumen and triple orifice were used.* A P23D Statham strain gauge was routinely employed and the impulses were recorded on an Offner direct recording unit.

Multiple samples of blood were withdrawn and analyzed for oxygen saturation by use of a cuvette oximeter. The results of these determinations were routinely confirmed by the method of Van Slyke[1] in two of the blood samples. During the procedure, the catheter was perfused as needed with a solution of 5 per cent dextrose in water containing 10 mg. of heparin and 500,000 units of penicillin per 1,000 c.c.

In each case the surgeon in charge was a pediatric cardiologist or a carefully supervised heart trainee. In children over 5 years of age the catheter was usually inserted into an antecubital vein; however, in younger patients the saphenous vein in the inguinal region was used. In those rare instances when the saphenous vein was too small the catheter was inserted directly into the femoral vein.

RESULTS

The size of the catheter used and the number and ages of the patients studied are presented in Table I. Of the subjects reviewed, 84 were under

*Goodale Lubin, Detroit, Mich.

2 years of age and 65 of these were under 1 year of age. A No. 7 catheter was usually employed, but the majority of the youngest patients would accommodate no larger than a No. 5 catheter. The pulmonary artery was cannulated in 79 per cent of the procedures. In the entire group of infants under 2 years of age, this vessel was entered in 73 per cent of the cases,

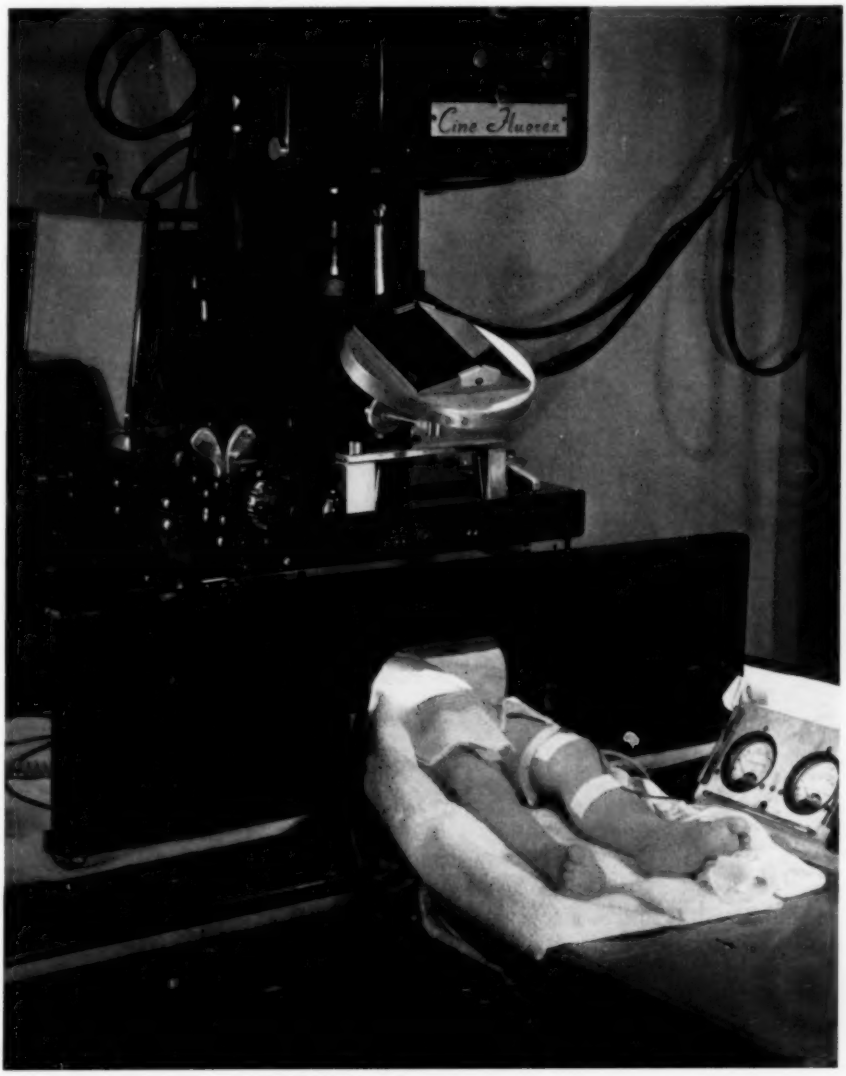

Fig. 1.—The screen enclosing the patient's trunk is made of ⅛ inch lead. The doors can be adjusted to make an aperture large enough for an infant's pelvis or small enough for an adult's arm. The legs are resting on a board attached to the x-ray table. The image amplifier with a split mirror can also be seen.

TABLE I. CATHETERS USED FOR RIGHT HEART CATHETERIZATIONS (218 CASES)

AGE IN MONTHS	TOTAL NUMBER OF PATIENTS	CATHETER SIZE					
		5	6	7	8	9	UNKNOWN
0-6	35	14	11	6	0	0	4
6-12	30	3	15	8	0	0	4
12-24	19	2	5	8	0	0	4
>24	134	2	22	52	44	2	12
Totals	218	21	53	74	44	2	24

TABLE II. STRUCTURES ENTERED DURING RIGHT HEART CATHETERIZATION (218 CASES)

AGE IN MONTHS	TOTAL NUMBER OF PATIENTS	PULMONARY ARTERY		LEFT ATRIUM		DUCTUS ARTERIOSUS		
		NUMBER ENTERED	PER CENT OF TOTAL	NUMBER ENTERED	PER CENT OF TOTAL	NUMBER ENTERED	NUMBER STUDIED	PER CENT OF TOTAL
0-6	35	21	60	18	52	0	0	–
6-12	30	21	70	17	57	5	6	83
12-24	19	19	100	8	42	0	0	–
Totals under 24	84	61	73	43	51	5	6	83
>24	134	110	82	41	31	13	16	81
Grand totals	218	171	79	84	38	18	22	82

TABLE III. ANALYSIS OF CLINICAL ACCURACY WITH AND WITHOUT DATA OBTAINED BY RIGHT HEART CATHETERIZATION (218 CASES)

AGE IN MONTHS	TOTAL NUMBER OF PATIENTS	NO. OF CORRECT DIAGNOSES WITHOUT CATH.	NO. OF PATIENTS UNDERGOING SURGERY	PER CENT ACCURACY	NO. OF CORRECT DIAGNOSES WITH CATH.	NO. OF PATIENTS UNDERGOING SURGERY	PER CENT ACCURACY
0-6	35	8	12	67	10	12	83
6-12	30	6	10	60	9	10	90
12-24	19	7	7	100	7	7	100
Totals under 2 years	84	21	29	72	26	29	90
>24	134	36	48	75	44	48	92
Grand Totals	218	57	77	74	70	77	91

but in those patients under 6 months in only 60 per cent (Table II). The left atrium was entered by way of an interatrial septal defect or the foramen ovale in 38 per cent of the studies (Table II). This figure was considerably higher (51 per cent) in infants under 2 years of age. Twenty-two of the patients undergoing studies had a preoperative diagnosis of patent ductus arteriosus. The descending aorta was entered via the ductus in 18 of these (82 per cent).

Seventy-seven of the patients had lesions that were considered correctable by surgery. Assuming that the findings at surgery represented the correct anatomical diagnosis, the clinical impression based upon history, physical examination, roentgenography, and electrocardiography was accurate 74 per cent of the time. The additional information gained by cardiac catheterization increased the accuracy of the diagnosis to 91 per cent (Table III).

DISCUSSION

It is significant that the ductus arteriosus could be cannulated in 82

per cent of the cases when patency of this structure was suspected. It is a well-known fact that based on hemodynamic data alone it is occasionally difficult to differentiate a patent ductus arteriosus from an interventricular septal defect.[2-4] The high degree of success which we have experienced in traversing the ductus lends support to the contention that right heart catheterization is the procedure of choice over the possibly more hazardous retrograde aortography in cases of this type.[5]

There was a total of three deaths resulting either directly or indirectly from the catheterization. This mortality rate of 1.4 per cent is extremely high when compared to published reports[6-12] (Table IV). The selection of the case material no doubt accounts in large measure for this disparity. In our series, many of the patients were suffering from intractable cardiac failure and some were terminally ill. A number of these, who very likely would not have survived if treated medically, were salvaged by early surgery. Of the three patients who expired, the end result in two would probably have been the same if the catheterization study had not been performed. One of these, a 10-year-old child who had severe aortic stenosis with intractable cardiac failure, expired during the procedure. At autopsy, in addition to aortic valvular stenosis, areas of myocardial infarction due to pronounced stenosis of the ostium of the left coronary artery were present. A detailed description of these findings has been presented elsewhere.[13]

The second patient had complete transposition of the great vessels and expired 18 hours after the catheterization. At autopsy, it was determined that the immediate cause of death was asphyxiation from aspiration of milk into the trachea. The third patient was a 10-month-old infant who was severely cyanotic and had severe valvular pulmonic stenosis. In retrospect, this patient should have had the benefit of emergency surgery as soon as the true nature of the abnormality was

TABLE IV. PUBLISHED SERIES OF RIGHT HEART CATHETERIZATIONS IN INFANTS AND CHILDREN (1950-1956)

INVESTIGATOR	YEAR PUBLISHED	AGE IN YEARS	NUMBER OF PATIENTS	MORTALITY	PER CENT MORTALITY
Schiffrin[6]	1950	1-5	33	1	0.33
Rojas[7]	1953	5	10	1	0.10
Zigler[8]	1954	0-½	120	4	0.69
		½-1	68		
		1-3	138		
		3-15	251		
Adams, Paul[9]	1954	2	53	0	0.00
Boesen[10]	1955	0-½	20	1	0.26
		½-1	16		
		1-2	1		
Boesen[11]	1956	0-½	29	0	0.00
		½-1	13		
		1-2	8		
Bouchard[12]	1956	1	35	0	0.00
Totals			795	7	0.88

established. The diminished blood volume resulting from cardiac catheterization probably caused reduction in an already precariously low cardiac output.

Several publications have recently appeared emphasizing the need for definitive studies in the younger age groups.[11, 14] In Boesen's series of 1,145 autopsies performed on patients dying with congenital heart disease, 50 per cent were under 1 year of age. He estimated that approximately one-third of the cardiac abnormalities found in these patients are now considered to be surgically correctable. Additional authors have emphasized congenital heart disease as a leading cause of infant mortality.[9, 15] It is for these reasons that we strongly believe that pediatric cardiologists must intensify their efforts toward the definitive diagnosis of congenital heart disease in the infant age group.

SUMMARY AND CONCLUSIONS

An analysis of 218 right heart catheterizations performed in infants and children at the Medical Center of the University of California at Los Angeles is presented. Eighty-five of the patients were under 2 years of age, and sixty-five of these were under 1 year of age. The pulmonary artery was entered in 73 per cent and the left atrium in 38 per cent of the studies. The procedure was found to be reasonably safe, even in small infants who are critically ill. Data obtained from cardiac catheterization increased the accuracy of diagnosis in the present study by 17 per cent. The authors believe that this procedure is an invaluable aid and that it should be utilized in selected cases regardless of the age or the physical condition of the patient.

We wish to express our gratitude to Dr. Edwardo Borda and Mrs. Margretta Reske for their aid in the translation of the Spanish and Swedish references.

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ACUTE UPPER RESPIRATORY DISEASE: CLINICAL AND BACTERIOLOGICAL RESPONSE TO SHORT-TERM TREATMENT WITH PENICILLIN V

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AMONG the various penicillins recently produced, phenoxymethylpenicillin, or penicillin V, described by Brandl, Giovannini, and Margreiter,[1] has physicochemical properties which would suggest effective absorption after oral administration. These physicochemical properties include high stability at pH ranges below 3.0, low solubility in acid medium, and easy and rapid conversion to the alkaline salt at neutral or alkaline pH.[2] Since all penicillins have been shown to be absorbed from the duodenum,[3, 4] penicillin V should produce a higher blood level than penicillin G after oral administration. Such superior blood levels have been shown[2, 5] and penicillin V has been reported to diffuse into all body fluids except noninflamed cerebrospinal fluid.[6] The spectrum of bacteria susceptible to penicillin V is comparable with that of penicillin G. Penicillin V has shown favorable clinical effects in the treatment of various infections,[5, 7, 8] and it has been shown to be an effective agent in the treatment of carriers of hemolytic streptococci in an institutional outbreak of scarlet fever.[9]

Reactions to the drug, minor or severe, have been infrequently reported.[10] In the face of growing numbers of reported instances of severe and fatal reactions to injected penicillin G, orally administered penicillin V shows promise as an equally potent and relatively nontoxic antibiotic.

This study reports on the clinical responses of, and bacteriological studies done on, 81 patients in a pediatric practice. Penicillin V was used in the treatment of various upper respiratory illnesses, and the dose used was higher than generally prescribed.

PLAN OF STUDY

The patients all came from a general pediatric practice in suburban Philadelphia. They were seen from early April until mid-September. Various types of upper respiratory illness were included in the study: tonsillitis, pharyngitis, otitis media, and cervical adenitis comprised the most frequently encountered diagnoses.

With the exception of four patients (parents suspected of being carriers), all patients herein reported were ill. The criteria for the severity of illness were not limited to the degree of fever, but they included tachycardia, anorexia, lassitude, toxicity, tenderness of nodes, and a general clinical evaluation of the patient.

Most of the patients were seen initially on a home visit, while the others were first seen in the office. Each was

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again fully examined in approximately 24 hours, either at home or in the office. Five or six days later a final examination and evaluation were made. All patients have been contacted by telephone or letter at the time of this writing to determine their present condition.

Penicillin V was given as the oral suspension* to all younger patients, in capsule form† to older children and parents. All patients weighing less than 30 pounds were given 125 mg. every eight hours for five days; all patients weighing more than 30 pounds were given 250 mg. every eight hours for four days although the generally accepted viewpoint is to continue the antibiotic for a week to ten days. In all cases treated, prescribed medication was limited to acetylsalicylic acid (to be given only if fever exceeded 103° F.), expectorant cough syrups, saline gargles, heat to swollen tender nodes, vasoconstricting nose drops, and controlled diet. With the exception of one case, to be described more fully, the only antibiotic prescribed was oral penicillin V.

For each patient, at the time of the initial examination, a swab of the pharynx, tonsillar fossa, or nasopharyngeal area, the choice depending on the clinical diagnosis, was taken and placed in a carrying tube containing trypticase soy broth. Another similar swab was made at the second examination, approximately 24 hours after the initial examination. When it was not practical to take the carrying tube directly to the laboratory, the tube was kept refrigerated at 36°-40° F. until the following day. All bacteriological studies were performed in the laboratory of the Bryn Mawr Hospital.*

The fluid in the carrying tube was studied in two ways:

A. An aliquot of 10 cubic microns was fixed and stained by the Gram technique. On this smear 100 bacteria were counted and the percentage of gram-positive cocci of this number was recorded. Strumia[11] has shown that the percentage of gram-positive cocci in a nasopharyngeal or pharyngeal smear can be used as an index of morbidity of upper respiratory disease in a community. Such a technique is a valuable screening procedure and serves as an adjunct to usual smear and culture procedures to be used during an epidemic and when laboratory facilities might be limited. The validity of this concept is supported by data of Kolmer and associates.[12]

In our community, at the time of this study, it was found that smears from ten apparently normal persons showed 58 per cent gram-positive cocci, with a standard deviation of 12 per cent (range 46 to 70 per cent). Smears from ten patients with clinically morbid throats showed 80 per cent gram-positive cocci, with a standard deviation of 14 per cent (range 66 to 94 per cent).

B. Another aliquot of 5 cubic microns was streaked on a blood agar plate and incubated for 24 hours. Cultures were then read, and the colonies were identified morphologically and were counted. On this morphological basis the relative abundance of the

*V-Cillin Suspension, supplied in two strengths, 125 mg. per teaspoon and 250 mg. per teaspoon, by Eli Lilly and Company.

†V-Cillin Capsules, 250 mg. each, supplied by Eli Lilly and Company.

*These studies were performed under a grant to the John S. Sharpe Research Foundation of the Bryn Mawr Hospital by Eli Lilly and Company, with helpful suggestions by R. S. Griffith, M.D.

various bacteria was reported as 4 plus (loaded), 3 plus (many), 2 plus (moderate), or 1 plus (few).

RESULTS

All patients took the medication well. In the six instances of regurgitation of the drug, parents were instructed to repeat the dose in one hour. In all six instances the patients retained the drug at the second trial.

The forms of upper respiratory illness encountered in this study are best shown in Table I.

TABLE I

PRIMARY DIAGNOSIS		ASSOCIATED CONDITIONS	
Tonsillitis	46	Cervical adenitis	14
Pharyngitis	35	Otitis media	3
		Varicella	2
		Scarlet fever	2
		Rubeola	1
		Asthmatic bronchitis	1
		Diabetes mellitus	1

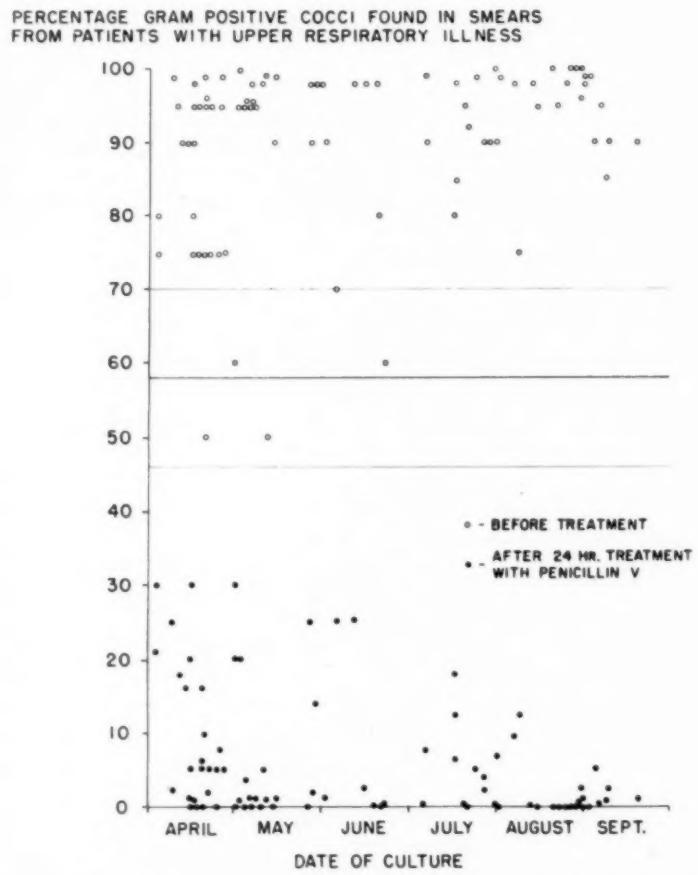

Fig. 1.—The reduction of percentage gram-positive cocci after twenty-four hours' treatment with penicillin V.

Two patients originally diagnosed as having tonsillitis developed varicella on the third day. One patient suspected of having pharyngitis developed the exanthem of rubeola on the fourth day. Two patients suspected of having pharyngitis developed the typical signs of scarlet fever, one on the second day, the other on the third day, after treatment had been started. Except for the associated conditions shown in Table I, there were no other complications of the primary condition.

Bacteriological Studies.—

Analysis of smears: As indicated above, for each smear taken before treatment and 24 hours later, 100 bacteria were counted, and the percentage of gram-positive cocci was recorded. The results of these counts are shown in Fig. 1, on which the open circles represent the pretreatment percentages, and the solid dots represent percentages found in smears taken 24 hours later.

Fig. 1 shows clearly that most of the cases studied were morbid according to the criteria of this technique: 76 of 81 cases showed percentages of gram-positive cocci which were above the standard deviation of the procedure (70 per cent), and 79 of 81 cases showed percentages above the mean (58 per cent). The heavy horizontal line at 58 per cent represents the mean, while the lighter lines at 46 per cent and 70 per cent, respectively, represent the standard deviation.

Comparison of the percentage of gram-positive cocci in the second smear

TABLE II. NUMBERS OF PATIENTS FROM WHOM VARIOUS ORGANISMS WERE RECOVERED

	BEFORE TREATMENT ABUNDANCE OF GROWTH					24 HOURS AFTER TREATMENT WAS STARTED ABUNDANCE OF GROWTH				
ORGANISM	4 PLUS	3 PLUS	2 PLUS	1 PLUS	TOTAL	4 PLUS	3 PLUS	2 PLUS	1 PLUS	TOTAL
Streptococcus pyogenes (beta)	7	10	8	5	30	2	1	–	–	3
Diplococcus pneumoniae	4	11	18	12	45	6	–	–	–	6
Streptococcus pyogenes (alpha)	2	14	11	8	35	8	–	–	–	8
Diplococcus pneumoniae and *Streptococcus pyogenes* (alpha)	–	8	5	7	20	7	–	–	–	7
Micrococcus pyogenes (beta-albus)	10	4	3	2	19	9	3	–	–	12
Micrococcus pyogenes (beta-aureus)	–	2	–	–	2	1	1	–	1	3
Escherichia coli	8	7	3	1	19	11	6	3	2	22
Neisseria pharyngis	15	22	6	3	46	36	17	13	2	68
Streptococcus pyogenes (gamma)	–	3	6	1	10	8	5	–	–	13
Micrococcus pyogenes albus *Micrococcus tetragenes* Diphtheroids	5	23	10	1	39	13	1	–	–	14

as contrasted with the percentage from the pretreatment smear shows a consistent and marked decrease. One factor which contributed to the tremendous change in percentage observed in some cases was the fact that in many instances the total bacterial population obtained on the second smear was markedly decreased. In no case does the percentage of gram-positive cocci in the second smear exceed the lower limit of the standard deviation (46 per cent).

Analysis of cultures: The results of the cultures are best shown in Table II.

It will be noted that the most frequently identified pathogenic bacteria were hemolytic streptococcus, pneumococcus, *Streptococcus viridans,* or some combination of these. Whereas these bacteria were not completely eliminated in all second cultures, the abundance of their growth was in all cases substantially reduced. A marked decrease in the combined incidence of these pathogenic bacteria is also shown in the second culture.

Table III shows the percentage of frequency of isolation from the 162 cultures of the various organisms before and after treatment. A substantial reduction in the recovery of pathogenic organisms is noted.

Clinical Evaluation.—At the initial examination, 77 of the patients were ill; 4 patients were parents suspected of being carriers. Actually the throat swabs of all four yielded hemolytic streptococcus on culture.

The initial and subsequent temperatures are shown in Table IV.

TABLE III. INCIDENCE OF VARIOUS BACTERIA IN CULTURES

ORGANISM	PERCENTAGES	
	BEFORE TREATMENT	24 HOURS AFTER
Streptococcus pyogenes (beta)	19	2
Diplococcus pneumoniae	28	3.7
Streptococcus pyogenes (alpha)	22	5
Diplococcus pneumoniae and *Streptococcus pyogenes* (alpha)	12	4
Micrococcus pyogenes (beta-albus)	12	7
Micrococcus pyogenes (beta-aureus)	1	2
Escherichia coli	12	14
Neisseria pharyngis	28	41
Streptococcus pyogenes (gamma)	6	8
Micrococcus pyogenes albus *Micrococcus tetragenes* Diphtheroids	24	9

TABLE IV. TEMPERATURE CHART OF 81 PATIENTS IN THIS STUDY

	UNDER 100° F.	100° TO 102° F.	OVER 102° F.
Initial temperature	4	21	56
24 hours later	39	41	1
48 hours later	75	5	1

Of the six patients who still had fever after 48 hours of treatment, five had childhood diseases as outlined above. One patient who had been diagnosed as having pharyngitis, and from whose throat hemolytic streptococcus was recovered before treatment, did not improve after 48 hours' treatment with penicillin, although his second culture did not again yield hemolytic streptococcus. This patient was then given novobiocin for 48 hours, after which he had shown no response to treatment. He was then given chloramphenicol palmitate, and he was

afebrile and clinically improved 12 hours later. This child subsequently developed a chronic tonsillitis and did not really become entirely well until after his tonsils and adenoids had been removed.

Except for the children with exanthematous disease and the patient above, all patients (75 of 81) were well at the six-day follow-up.

There were 14 patients with cervical adenitis. It was striking that 12 of these patients showed no tenderness of nodes at the 24-hour checkup, and none of them showed tenderness of nodes at the six-day follow-up.

With the exception of the children with exanthematous diseases, and the one patient described above who showed no response, there was only one other patient who did not demonstrate a marked clinical improvement within 24 hours. She was a girl with associated asthmatic bronchitis. At the 24-hour checkup, she still had fever of 101° F., and wheezes were heard in all lung fields. She was placed on prednisone, 5 mg. four times daily, and she was clinically improved within another 24 hours. Recovery was uneventful.

At the 24-hour checkup, all 74 remaining patients showed a striking clinical improvement. This was evidenced by a regression of all positive physical findings of the infection: drop in temperature elevation, decrease in tachycardia, lack of pain, improved appetite, and absence of a toxic appearance. Of these 74 patients, 35 still had a low-grade fever at the 24-hour checkup; however, all these children looked better and appeared improved by clinical evaluation.

At the time of this writing there have been no untoward effects of treatment with penicillin V in any of these patients. There have been no cases of nephritis or rheumatic fever in this group. The incidence of necessity for removal of tonsils and adenoids has not been any higher in this group than in the community at large. There have been no delayed urticarial reactions.

Reactions.—There were no severe reactions. There were two cases of maculopapular eruptions occurring on the third and fourth days, respectively, of treatment. In both instances the rash disappeared spontaneously within 36 to 48 hours after discontinuation of the drug. There were no cases of gastrointestinal disturbance or stomatitis or perianal dermatitis. One patient known to have developed urticaria after a dose of injected penicillin G took the penicillin V orally without evident reaction.

DISCUSSION

Aside from the factor of increased numbers of reactions to injected penicillin G as compared with orally administered penicillins, there is the obvious consideration, especially in pediatric practice, of painful injections. Should penicillin V prove as effective orally as injected forms of penicillin, it will prove a boon to the practicing pediatrician whose appearance to many of his younger patients is immediately and tearfully associated with a "shot." With the additional injections recently added to the prophylactic immunization program, the need for improving rapport of the pediatrician with his younger patients becomes increasingly evident. A truly effective oral penicillin will be a welcome addition to

available drugs. Most patients can take drugs orally. Aside from the moribund patient who obviously needs special handling, most patients who "can't" take drugs by mouth are those who refuse to for one reason or another. These patients will usually cooperate when they, and their parents, are approached and instructed properly. In our study, no patient refused the drug. The ages of our patients ranged from 7 months to adulthood.

The dose of penicillin V used in this study was arbitrarily set. The choice of 250 mg. every eight hours for patients weighing more than 30 pounds was based partly on the study reported by Wehrle, Feldman and Kuroda.[7] These authors found an increased relapse rate among carriers of hemolytic streptococcus when lower doses of penicillin V were used. For this study we felt that to err on the side of overdosage would be prudent.

SUMMARY

1. Clinical and bacteriological studies on 81 patients with upper respiratory diseases who were treated with oral penicillin V are reported.

2. Excellent clinical responses were observed in 75 of the 81 patients. Of the 6 who did not exhibit a satisfactory clinical response, 5 were initially incorrectly diagnosed and were actually suffering from exanthematous diseases. One patient showed no clinical response at all.

3. A procedure of studying inocula from nasopharyngeal and pharyngeal smears stained by the Gram technique is described. This technique has been valuable for screening purposes when laboratory facilities are limited or burdened.

4. Nasopharyngeal and pharyngeal smears from patients who had received penicillin V for 24 hours showed a significant decrease in gram-positive cocci as compared with smears taken before treatment was started.

5. Cultures made from swabs taken from the nasopharyngeal and pharyngeal areas of patients who had received penicillin V for 24 hours showed a significant decrease in pathogenic organisms as compared with cultures taken before treatment was started.

6. Among 81 patients who received penicillin V orally for 4 to 5 days there were no serious reactions. There were two instances of maculopapular rashes which subsided uneventfully.

7. In this study of 81 patients with upper respiratory diseases, oral penicillin V has proved to be an effective and safe antibiotic.

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STUDIES IN HUMAN REPRODUCTION

III. The Frequency of Congenital Malformations in the Offspring of Nondiabetic and Diabetic Individuals

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In 1885 Lecorché[1] reported hydrocephalus in the offspring of two diabetic women. Since that time, there has been a continuing interest in maternal diabetes mellitus as a possible factor in the etiology of congenital malformations. Although a few authors have reported no increase in the incidence of anomalies[2-6, 42] among infants born to diabetic women, most students of the subject believe that the malformation rate is higher.[7-15]

Incidence of Malformations in a Control Population.—Ideally, in order to state that malformations occur with unusual frequency in infants born of diabetic mothers, it would be necessary to know the incidence of congenital defects in the offspring of a comparable, nondiabetic group. Unfortunately, even in the general population, it is difficult to ascertain accurately the malformation rate. In the first place, there is no universal agreement as to what constitutes a congenital defect. For example, some authors include such conditions as atelectasis, "heart murmurs," undescended testicles and hydrocele of the cord.[16] On the other hand, others list only those anomalies which are incompatible with life.

The source of the data also materially influences the reported incidence of anomalies. One author may base his frequency on information obtained from birth[30, 31] or death certificates, while another may use hospital records, and thereby find a considerably higher incidence. For example, Lilienfeld and associates[17] correlated data on birth certificates with information from hospital records, and discovered a discrepancy of 34 per cent between the two sources.

Who examines the infant is obviously of importance, too. Frequently an investigator relies upon records made by others. A higher incidence of defects has been reported in those studies in which a particularly interested observer has examined each infant.

The age of the fetus at the time of its examination is also important.[16, 31] One observer may report only upon term fetuses. Others have included every fetus weighing over 500 grams.[16] When these smaller fetuses are included, a higher malformation rate results.

Furthermore, all defects are not discovered at birth. For example, McIntosh and associates[16] studied the time of the diagnosis of the defects of 386 congenitally malformed infants who survived the neonatal period.

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The anomalies of 43.2 per cent of the infants were diagnosed at birth, 38.7 per cent were found between birth and 6 months of age, 15.3 per cent between 6 and 12 months, and 2.8 per cent were not diagnosed until after 12 months of age.

The reported incidence of malformations also varies considerably depending on whether dead or living infants are examined. This is due principally to the fact that autopsy information contributes considerably to the diagnosis of malformations. McIntosh and associates[16] analyzed data from 5,739 consecutive deliveries. They included all fetuses weighing over 500 grams. Autopsies were performed upon 85 per cent of all infants who were either stillborn or died neonatally. These workers presented the figures given in Table I.

TABLE I

CONDITION OF INFANT	MALFORMATION RATE (PER CENT)
Born alive and surviving neonatal period	7.0
Antepartum death	13.6
Intrapartum death	23.3
Neonatal death (died within 1 month of birth)	29.6
Dead between 1 and 12 months	70.6

Thus, McIntosh and associates discovered malformations in as many as 30 per cent of infants who died during the perinatal period. On the other hand, the incidence of congenital defects in all infants (both living and dead) in the general population, according to 15 reports in the literature (Table II), varies from 0.9 to 7.5 per cent.[16, 18-31] The average incidence of malformations found in these studies was about 2 to 3 defective infants per hundred births. Because of the low incidence of diabetes mellitus in women during the reproductive era,[32] one might use these figures given for the general population in lieu of those for a nondiabetic population, particularly since there is paucity of data on the latter group.

TABLE II. INCIDENCE OF CONGENITAL MALFORMATIONS IN INFANTS BORN IN GENERAL POPULATION, BASED ON CLINICAL AND AUTOPSY INFORMATION

AUTHOR	INFANTS	
	NUMBER	PERCENTAGE WITH MALFORMATIONS
McIntosh et al.[16]	5,739	7.5
Tholen[18]	1,833	3.6
Javert and Stander[19]	27,000	2.9
Malpas[20]	13,964	2.1
Landtman[21]	3,593	2.0
Lucy[22]	11,881	1.7
Stevenson et al.[23]	29,024	1.7
Greenberg et al.[24]	6,358	1.5
Carter[25]	14,283	1.4
Miller[27]	4,095	1.4
Stark[28]	4,444	1.4
Naujoks[29]	17,800	1.3
DePorte and Parkhurst[30]	273,604	1.2*
Wallace et al.[31]	162,400	0.9*

*Based on information from birth certificates.

Incidence of Malformations in Offspring of Diabetic Women.—Since autopsy data are most clear cut, let us consider them first. There are a few reports on the malformations discovered at autopsy of infants born to diabetic mothers. These are listed in Table III. Miller[33] found congenital

TABLE III. INCIDENCE OF CONGENITAL MALFORMATIONS IN INFANTS OF DIABETIC WOMEN, BASED ON AUTOPSY INFORMATION

AUTHOR	INFANTS	
	NUMBER	PERCENTAGE WITH MALFORMATIONS
Miller[33]	19	31.5
Warren and LeCompte[34]	50	18.0
Cardell[35]	24	25.0

malformations in 31.5 per cent of 19 cases. Warren and LeCompte[34] discovered anomalies in 18 per cent of 50 infants, and Cardell[35] found defects in 25 per cent of 24 infants. These percentages do not differ significantly from those for the incidence of anomalies in dead infants in the general population.[16, 23] Furthermore, Cardell found a 20.2 per cent incidence of anomalies in his control group of 99 infants born to nondiabetic women. The autopsies upon the latter infants were performed in his hospital during the same period of time in which the infants of the diabetic women exhibited a 25 per cent incidence of defects. The difference in the malformation rates in the infants of the diabetic and nondiabetic mothers in Cardell's report is not statistically significant. From these observations it would seem that the congenital malformation rate determined by autopsy is not unusually high in the infants of diabetic women. However, most articles giving malformation rates in the offspring of diabetic women use an over-all incidence and do not indicate separate rates for living and dead infants. Furthermore, in many of the reports it is impossible to determine how many of the infants had postmortem examinations. Hence, these reports are listed under the title, "Incidence of Malformations in Infants of Diabetic Women, Based on Clinical and Autopsy Information" (Table IV). This table gives the most recently reported figures of each author, except for White[36] as her most recent data include every deviation from the normal discovered in children followed to 20 years of age, as will be discussed later. The incidence of malformations ranges from none to a high of 16 per cent. If one weights the figures for the size of each series reported, the average is 5.3 per cent. This latter figure probably should be compared with an average incidence of anomalies in the general population reported in the literature as being between 2 and 3 per cent (Table II). White and Hunt[8] (Table IV), who reported the highest rate of malformations (16 per cent) in the offspring of diabetic women, compared this frequency of anomalies with an over-all hospital incidence of malformations of 1.8 per cent. While this 16 per cent appears to be a high rate of malformations, it must be evaluated in the light of several factors. First, the incidence of fetal death in the series of diabetic mothers was 14 per cent. This is at least three times the anticipated incidence of fetal death in the general population.[37] As previously indicated, the frequency of anomalies among all dead infants approaches 20 per cent.[16, 23, 35] Hence, the high infant death rate in White's diabetic group would tend to increase the reported anomaly rate.

TABLE IV. INCIDENCE OF CONGENITAL MALFORMATIONS IN INFANTS OF DIABETIC WOMEN, BASED ON CLINICAL AND AUTOPSY INFORMATION

AUTHOR	INFANTS	
	NUMBER	PERCENTAGE WITH MALFORMATIONS
White and Hunt[8]	125	16.0
Barns[9]	40	10.0
Peel and Oakley[10]	142	6.3*
Koller[11]	136	4.4*
Andersson[12]	47	4.3
Hurwitz and Higano[13]	140	3.5
Jones[14]	162	3.1†
Skipper[15]	136	3.0
Reis et al.[5]	163	1.2
Given et al.[42]	106	0.95
Hall and Tillman[6]	104	0.0

*"Serious anomalies."
†Anomalies incompatible with life.

It might be suggested that lethal anomalies in White's series were responsible for the high fetal mortality. Actually, she stated that only 12 per cent of her dead infants had lethal anomalies. Hence, White's high death rate was not due to congenital malformations. In a later report,[38] she states that in a series of 439 viable infants (weighing more than 960 grams), the fetal death rate was 18 per cent. Here 8 per cent of the dead babies exhibited anomalies. This is not an abnormally high incidence of defects for dead infants, regardless of whether the diagnosis of the anomaly was made clinically or at autopsy.[16, 35] Furthermore, when autopsies are performed, obviously, more anomalies are discovered. Although White does not give the percentages of infants which were autopsied, it may well have been high in her diabetic group. If this were so, it would tend further to increase the reported incidence of anomalies in this group.

More recently, White[32] has stated, "Congenital defects have occurred in 80 per cent of the infants of our diabetic mothers compared with the expected incidence of 1.8 per cent." She wrote to us[36] that this 80 per cent incidence was arrived at as follows: "Many of the abnormalities have been revealed by subsequent visits of these children, during x-ray examinations, etc. Every deviation from the normal has been counted in the figure of 80 per cent, and included are such slight abnormalities as a nevus, shovel rib, ear nodules and many things which are overlooked unless the observer is actually watching for defects. I do not think that comparable studies have really been made on children of normal women. The figure was based on a pilot study which Sidney Gellis personally conducted not only on the newborn, but on children of diabetic mothers up to age twenty." We, also, know of no study of children born to nondiabetic women which can be compared with this pilot study which yielded an 80 per cent incidence of anomalies.

Furthermore, because the infants of diabetic women often present difficulties in management, they receive an unusual amount of attention, and more accurate records are kept of their condition. This would tend to reveal malformations in more of these infants than would be the case in a general hospital population. In view of this fact, an adequate control series would need to be one in which the infants received similar care and equally complete recording of historical data. Such a control series of infants undoubtedly would reveal a higher incidence of defects than one taken from the usual hospital records.

Another factor influencing the incidence of congenital malformations is maternal age. There is accumulating evidence to indicate that the malformation rate increases with maternal age, particularly after 30 years of age.[26, 39] Koller[11] found a high incidence of congenital anomalies in the infants of diabetic women, but only in those whose disease began in childhood and was of long duration. Neither Koller nor any other author was able to separate the factors of maternal age and the duration of the diabetes. Similar questions arise regarding the observations found in the other reports listed in Table IV.

Reid,[40] of the Boston Lying-in Hospital, studied the incidence of lethal anomalies found in a series of 289 infants of diabetic mothers cared for at the Joslin Clinic. Of these, 7, or 2.4 per cent, had such anomalies, compared to an incidence of 0.75 per cent observed among the general population of infants born at the same hospital. Reid carefully defined a lethal anomaly as "a malformation which is sufficient to explain intrauterine death, or is incompatible with extrauterine existence for more than a limited period." Reid's figures would appear to be the best evidence currently available to indicate that the infants of diabetic mothers may have a higher incidence of anomalies incompatible with life than do infants in the general population. However, it should be restated that the death rate of infants of diabetic mothers is at least three times greater than that in the general population. Thus, even if the autopsy rate is the same in infants of diabetic and nondiabetic women, there would still be three times as many autopsies performed on infants of diabetic mothers, yielding a correspondingly higher anomaly rate. In view of the fact that diabetic women receive special care, it also is quite possible that the autopsy rate will be higher in their offspring than would be the case in those used as a control group.

Malformations in the Offspring of Diabetic Men.—It is well known that diabetes mellitus may be familial.[32] White[32] has suggested that the malformations which occur in the offspring of diabetic mothers are also genetic in origin. This raises the possibility that diabetes mellitus in men might also increase the incidence of malformations in their offspring. Koller[41] interviewed 55 diabetic men regarding the occurrence of congenital malformations in their children. Their wives gave birth to a total of 123 infants. Two of these infants suffered from congenital dislocation of the hips, giving a malformation incidence of 1.6 per cent.

One of us (A. R.)[41] interviewed a random series of 168 married diabetic men attending the outpatient diabetes clinics of the Hospital of the University of Pennsylvania and the Philadelphia General Hospital. These patients were questioned regarding the development of their offspring. An equal number of married, nondiabetic men attending two outpatient dental clinics were interviewed in a similar manner.

The wives of 140 of the diabetic men had 463 pregnancies lasting 28 weeks or longer. Three of the offspring presented congenital anomalies (hydrocephalus, omphalocele, clubfoot), an incidence of 0.65 per cent. One hundred and fifty-four wives of the nondiabetic men had 350 pregnancies lasting 28 weeks or longer. One had a malformed child (hydrocephalus), an incidence of 0.29 per cent. The difference in these two frequencies is not statistically significant. Thus, these observations, and Koller's report, supply no evidence to indicate that the offspring of diabetic men exhibit an unusual frequency of malformations.

SUMMARY

1. The reported incidence of congenital malformations in the general population is influenced by a number of factors such as: (a) definition of congenital malformation; (b) source

of the statistics; (c) who diagnoses the anomaly; (d) methods employed in arriving at diagnosis, i.e., inspection, x-ray, etc.; (e) maturity of fetus at the time that the diagnosis is made; (f) whether the infant is alive or dead when examined; (g) autopsy incidence.

2. The above factors, as well as the lack of comparability of the various reports in the literature, make it difficult to establish a malformation rate for the general population which would be satisfactory to all students of the subject. The same considerations make it equally difficult to ascertain the incidence of congenital anomalies in the infants of diabetic patients. The incidence of anomalies in the infants born to diabetic women is reported in the literature as ranging from none to 16 per cent, with an average rate of approximately 5.3 per cent. The frequency of defects in infants in the general population probably averages 2 to 3 per cent.

3. The infants of the diabetic women reported in the literature appear to have been observed more closely than those used as controls. This would probably lead to a higher reported incidence of malformations in the infants of diabetic mothers.

4. The mortality rate of infants of diabetic women is 3 to 5 times that of infants of nondiabetic women. The malformation rate in dead infants, of both diabetic and nondiabetic women, is 6 to 8 times higher than in living infants in the general population. Hence, the higher mortality rate in the offspring of diabetic women plays a role in explaining the high malformation rate in their children.

5. The high mortality rate of the infants of diabetic women is not due primarily to congenital anomalies.

6. When the above factors are taken into consideration, the reported high frequency of malformations in the offspring of diabetic women losses much of its significance.

7. No evidence could be found in the literature to indicate that congenital anomalies occur with unusual frequency in the offspring of diabetic men.

8. The incidence of congenital malformations was studied in 463 offspring of a series of 140 diabetic men. It did not differ significantly from that found in 350 infants of 154 nondiabetic men.

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CEREBRAL ANGIOMATOSIS

Report of a Case in an Infant, With a Review of the Literature

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THE diagnosis of cerebral angiomatosis in a 7-week-old infant prompted a review of the literature in an attempt to delineate better the symptoms and signs that should alert the physician to the possibility of arteriovenous malformations in the child. A fair proportion of these abnormalities are amenable to surgery and, when they are, surgery should be performed before irreparable damage has taken place.

REVIEW OF LITERATURE

The first presumptive clinical diagnosis of a cerebral angioma was made in 1898 in a patient with left spastic hemiparesis and a bruit, audible over the entire head. Since the introduction of angiography it has become evident that intracranial angiomas or, more correctly, arteriovenous malformations are not rare.

According to Paterson,[1] most intracranial angiomas are to be found on the lateral aspects of the cerebral hemispheres and in particular near the Sylvian fissure. Less commonly they are situated on the medial aspects of the hemispheres, in the corpus callosum, the orbits, within the ventricles, in the posterior fossa, or near the midline in basal structures. Noran[2] gave a pathological classification of the intracranial vascular tumors and malformations closely correlated with the types of vascular structure, thereby increasing the understanding of the relationship between their clinical and their pathological aspects. Dandy[3] was one of the first to describe cerebral arteriovenous angiomas. In his 8 cases, focal epileptic attacks were present and a gradually progressive motor or sensory hemiplegia of the affected side developed. Cerebral hemorrhage, the principal cause of death, occurred in about 40 per cent.

In the same year, Cushing, and Baily and Dandy,[3, 4] reported 22 cases of which 17 were arterial angiomas with arteriovenous connections and 5 were carotid cavernous fistulas. The most common symptom was headache. Epileptiform seizures were reported in 6 patients, nausea and vomiting was observed in 8, bruit in 5, and intracranial calcification in 4. The youngest patient was a 6-year-old girl with convulsions, mental retardation, and right-sided paresis and ataxia.

In 1936 another monograph appeared, in one section of which Toennis[5] considered a number of patients with arteriovenous aneurysms. He recorded a series of 22 cases in some of which a diagnosis by arteriography

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was made before operation. An audible bruit was found in 4 cases and several had Jacksonian attacks.

In 1937, Jaeger, Forbes, and Dandy[6] described the occurrence of a bilateral congenital cerebral arteriovenous communicating aneurysm diagnosed at autopsy in a 3-year-old child.

In 1948, Olivecrona and Riives[7] reported 42 cases of arteriovenous aneurysm. The cardinal signs were epileptic fits, subarachnoid hemorrhage, and hemiplegia. A systolic bruit was heard in 8 cases with characteristic calcifications. The first symptoms usually occurred during the second or third decade.

In 1953, MacKenzie[8] presented 50 cases where the presence of a cerebral angioma had been proved by arteriography. The diagnosis was made in this series between the ages of 12 and 59 years. Analysis of the presenting complaint showed this to be epilepsy in 16 cases, hemorrhage in 15, headache in 12, hemiparesis in 6, and a pulsating exophthalmus in one. One patient with a left-sided angioma had a right-sided infantile hemiplegia. According to the studies of MacKenzie,[9] only 10 per cent of the patients had a relevant symptom in the first decade of life, in 70 per cent before the age of 30. About 90 per cent were discovered before the age of 40. If there has been no recent rupture, the spinal fluid is normal. X-rays of the skull and electroencephalogram are often normal.

In 1953, Toennis and Lange-Cosack[10] also described 76 patients with arteriovenous angiomas of the brain. In 55 patients chronic psychopathic syndromes were seen. In 35 cases mental deterioration occurred. All patients with frontal, temporal, and diffuse angiomas as well as a high percentage of the centroparietal angiomas had lasting psychic changes. There also were frequent epileptic attacks. The treatment of choice was total extirpation before cerebral atrophy had developed. Ligation of the carotid artery was discarded as an inadequate procedure.

In 1956, Walker[11] studied a series of 84 cases of intracranial vascular malformations verified by angiography in 9, operation in 76, and autopsy in 17. Approximately 80 per cent of the patients had a history of symptoms for more than two years. Epilepsy was the presenting complaint in 40 of the 64 patients with supratentorial lesions. In 26 cases the seizure was of the Jacksonian type. The next most common symptom was a neurologic deficit—in 13 cases a hemiparesis—usually of the spastic type. Subarachnoid hemorrhage was manifest in 14 cases. Intracranial hypertension occurred in 2 patients associated with cranial nerve palsies, notably a sixth nerve paralysis. Noises in the head were noted by 8 patients. In 5 of these cases a bruit could be heard on auscultation. Hemorrhage was reported in 20 per cent. Other authors reported hemorrhage as the first symptom in a high proportion of patients with intracranial vascular anomalies, e.g., 56 per cent in the series of 24 cases of Gould, Peyton, and French,[12] and 54 per cent in the presentation of 37 cases by Anderson and Korbin.[13]

Crawford and Russell[14] discussed 20 cases of spontaneous cerebral and cerebellar hemorrhage in 15 children and adolescents and 5 adults due to small arteriovenous or venous hamartomas of the brain. Clinically the

cases presented either as catastrophic apoplexies or, less acutely, simulating rapidly growing neoplasms.

Potter[15] reported 58 cases of cerebral angiomas verified either at operation, by angiography, or at autopsy. In his series, only 22 per cent presented a cranial bruit and in only two were there extracranial vascularities. Hemorrhage occurred in 82 per cent and was the presenting symptom in 58 per cent.

In a study of 148 patients with spontaneous subarachnoid hemorrhage, Faleoner[16] pointed out that arteriovenous malformations are the second most common cause of subarachnoid hemorrhage, accounting for about 5 to 10 per cent. More malformations manifest themselves by epilepsy than by hemorrhage. The association of epilepsy, the occurrence of bleeding in childhood, or a history of attacks of bleeding extending over many years is more suggestive of malformation than of aneurysm. All his 12 patients who underwent operation survived and were benefited by the surgery.

A series of 110 patients with intracranial angiomas have been seen by McKissock[17, 18] at the National Hospital and St. George's Hospital, London. The cardinal symptoms were those due to a subarachnoid or intracerebral hemorrhage (42 per cent), with or without epilepsy and periodic migrainous headaches. The youngest patient to develop epilepsy in this series was a 1-year-old child. In some cases a progressive hemiparesis with insidious onset was seen. Intracranial bruit was present in 38 per cent, focal neurological signs in 69 per cent, while papilledema and dementia were not common. Associated vascular anomalies and complications were cirsoid aneurysms of the scalp, intracranial aneurysms, and chronic subdural hematomas. Two patients of this series had arteriovenous malformations involving the orbit with increasing proptosis of the affected eye and a pulsating bruit referred to the ear on the same side. Total excision was reported as the ideal form of treatment. In 35 patients, McKissock was able to remove the malformation completely. Ligation of cortical feeding vessels was of value in certain cases but ligation of the common or internal carotid artery did not appear to be of value in treatment. Also the results of radiotherapy were disappointing.

The frequency of a bruit varied in reported series from 15 per cent[12] to 50 per cent,[8] averaging 22 per cent. A systolic bruit is audible in a certain proportion of normal infants and young children, also in some patients with small saccular aneurysms,[19] over certain vascular tumors, in carotid-cavernous fistula,[20, 21] and contralateral to thrombosed cervical carotid artery.[22] Hamburger[23] stated that cephalic murmurs in children are prevalent particularly during the second year of life when they occur two and a half times as frequently as in the first year of life. Ford[24] attributed these benign murmurs to anemia. The youngest case in the series of Gould, Peyton, and French[12] was diagnosed at the age of 6 weeks. The parents had observed a rapid growth of the head. The arteriovenous malformation was in the left cerebellar hemisphere where it had produced a block of the flow of the cerebrospinal fluid.

Logue and Monekton[25] reported 9 patients with angiomas in the posterior fossa. Two were located in the cerebellum with cerebellar apoplexy, sixth nerve involvement and scattered pyramidal tract signs. The remaining seven were located in and about the brain stem. Of these 7 patients, 4 had subarachnoid hemorrhage, 2 progressive neurological signs, and 1 acute obstructive hydrocephalus. The general neurological picture was that of a progressive disorder of the third to the eleventh cranial nerves, symptoms of pyramidal tract involvement or cerebellar ataxia and tremor. Three patients had an intracranial bruit.

Rosner[26] reported 34 cases of cerebral palsy of which 33 were due to vascular anomalies. In these 33 children Rosner found cerebral venous angioma at the lower angle of the Sylvian fissure on one or both sides. Craniotomy was performed and the angiomatous vessels were cauterized with the electrocautery. The 29 children who survived the operation showed improvement of spasticity and athetosis as well as of epilepsy and of drooling.

A case of bilateral optic nerve atrophy and blindness of the left eye without any other signs or symptoms was presented by Band.[27] The cause was a cerebral arteriovenous aneurysm.

Laur[28] reported a giant cerebral angioma with anomalies of the great arteries and multiple saccular aneurysms in a 15-year-old boy who developed epileptic seizures at the age of 15. He had a right pulsating exophthalmus which had been present since birth; he also had an internal hydrocephalus, debility, and cardiac enlargement. Cerebral angiography revealed an arteriovenous aneurysm of the left hemisphere measuring 11.5 by 8 by 7 cm. and also saccular arterial aneurysms on the right side, together with anomalies of the circle of Willis and multiple aneurysms of the right internal carotid.

Groethuysen, Bickford, and Svien[29] gave a detailed analysis of the electroencephalogram in 18 patients with arteriovenous anomalies of the brain. They as well as Gillingham[30] and others reported that the diagnostic value of the electroencephalogram in evaluating suspected cases is limited. Low-voltage bilateral abnormalities in theta or delta range with one-sided predominance were found in the majority of arteriovenous anomalies. In view of the high localizing value of ictal and postictal focal electroencephalographic changes, the more frequent use of activation methods to induce a seizure was suggested.

Ferey[31] reported 10 cases of central angioma. In 5 patients the initial symptom was progressive hemiparesis; in 4 a complicating subarachnoid hemorrhage was accompanied by the rapid onset of focal signs, usually a hemiparesis. One patient only had epileptic seizures. This boy started to have monthly grand mal seizures at the age of 2 years. Nine patients had contralateral hemiparesis accompanied in 5 instances by sensory defects and in 4 by a partial or complete homonymous hemianopsia, by pupillary abnormalities in 3, ptosis and external ocular palsies in 4, and nystagmus in 2 cases. In only 2 of the 10 patients was an intracranial bruit heard. In 8 of the 10 cases the routine skull film was reported to be

normal. In 9 of the 10 patients the angioma was diagnosed by angiography and was thought to lie in the neighborhood of the thalamus, basal ganglia, and internal capsule. In one the diagnosis was made by post-mortem examination.

Rosenberg[32] presented a 4-month-old infant with alternating Jacksonian seizures, opisthotonus, and progressive hydrocephalus. Angiography revealed an arteriovenous malformation with communication between the left anterior cerebral artery and the great vein of Galen. Autopsy showed an angiomatous malformation on the medial aspect of the left cerebral hemisphere.

Arteriovenous malformations in the region of the pineal gland are rare. The first reported case of arteriovenous malformation drained by the vein of Galen was described by Jaeger, Forbes, and Dandy,[6] and reports of Alpers,[33] Oscherwitz,[34] Boldrey,[35] Olivecrona,[7] Gillingham,[30] and French[36] followed. French and Peyton[36] reported 5 cases of arteriovenous malformation in the region of the pineal gland. Although these are unfavorable for removal because of their location, nevertheless they are operable when it is possible to demonstrate their arterial supply by angiographic studies. The only signs may be increased intracranial pressure with slowly developing hydrocephalus.

In 1949, Norlen[37] reported 10 patients with arteriovenous anomalies of the brain in whom radical removal resulted in restoration to normal in 7, and in improvement of neurologic defects in 3. In one patient mental function was reported to be improved some months after operation.

Bassett[38] presented 18 cases of cerebral arteriovenous anomalies. He recommends direct surgical attack and does not believe that irradiation has a place in treatment.

Pilcher, Meacham, and Cobb[39] reported 11 cases of intracranial angiomatous malformations and recommended surgical removal if the lesion is accessible. After occlusion of the arterial radicals, the venous tributaries are clipped and the lesion removed. Lobectomy as an alternative plan of removal may be used when the angioma is located in the frontal or occipital lobe.

The works of Olivecrona and Riives,[7] of Norlen,[37] of McKissock,[40] of Jaeger,[41] and of Toennis and Lange-Cossack[10] indicate that the treatment of choice is now total excision of the malformation. Where this is not practicable, as in deep-seated lesions, the feeding artery can be occluded and any associated intracerebral clot evacuated.

CASE REPORT

A 7-week-old white female infant entered the hospital on June 25, 1957, because of a progressive swelling of the right eye. The child was born after a full-term pregnancy that was normal except for a mild kidney infection. Delivery was with low forceps. Birth weight was 8 pounds 11 ounces. There was no cyanosis or respiratory difficulty. Immediately after delivery the mother noted a swelling of the right eye. This was thought to be due to the forceps. However, the swelling increased and the eye deviated to the right and appeared prominent. On the day of admission the infant had twitchings of her face, mouth, and arms. These twitchings lasted up to ten minutes and had occurred about six times prior to admission. The child held

her head to the right side and seemed more sleepy than usual. There had been no vomiting.

Family history was not contributory. The four siblings aged, respectively, 10, 8, and 3 years, and 16 months were well.

Physical examination revealed a 7-week-old infant with an obvious deformity of the right eye. The head was held toward the right. Head circumference was 40.5 cm. The anterior fontanel was bulging and measured 5 by 7 cm. The posterior fontanel was also bulging and measured 4 by 5 cm. The veins on both sides of the head, but particularly over the right hemicranium, were engorged. There was a small, soft swelling above the superior portion of the sagittal suture extending to the right. In addition, a soft discrete swelling on the right side of the forehead was noted and a diffuse soft swelling involving the bridge of the nose, the right supraorbital ridge, and the lateral portion of the right eye. A loud to-and-fro bruit was heard over the right side of the skull. This bruit could be obliterated by compression of the right carotid. The right eye was proptosed and showed chemosis of the conjunctiva. Both pupils were deviated to the right. The right pupil was irregular and larger than the left and reacted sluggishly to light. Fundoscopic examination revealed dilated veins; however, the margins of the discs were well defined and there was no evidence of papilledema. Examination of the chest was negative. The liver was palpable 2 cm. below the right costal margin. The deep tendon reflexes were normal, and no stiffness of the legs, back, or neck was noted. There was no limitation of motion. Temperature was 38.4° C., pulse 136, respiration 70, weight 8 pounds 14 ounces.

Examination of the blood revealed a hemoglobin of 6.9 Gm. per 100 ml., red blood cells 2,240,000 and a white cell count of 8,700. The hemoglobin was raised to 13.8 Gm. by a blood transfusion (135 c.c.). The urine was normal. Serum bilirubin was normal. Kahn and Kolmer tests were negative. Cerebrospinal fluid was slightly xanthochromic, with 81 red blood cells, and 24 white blood cells with 20 neutrophils and 4 lymphocytes, protein was 86 mg. per cent, glucose 44 mg. per cent. There were no tumor cells or organisms seen. A ventricular tap 8 weeks later revealed 214 mg. per cent protein. On subdural taps, bright red blood was obtained with icteric supernatant fluid. The smear showed crenated red blood cells. No organisms were seen on stained smear and the culture was negative. Biopsy of the tumor at the right side of the scalp was performed by Dr. Pieter A. de Vries. It showed a hemangioma.

Skull films and pneumoencephalograms revealed increased intracranial pressure. There was no definite evidence of internal hydrocephalus. However, external hydrocephalus appeared to be present and a communicating hydrocephalus was suspected. A small area of bone destruction in the right parietal bone was seen. A subsequent ventriculogram revealed an internal hydrocephalus. A cerebral angiogram (Fig. 1) disclosed an arterial venous malformation which shunted the blood received from the internal carotid artery away from the right cerebral hemisphere. There appeared to be two parts to this malformation. One was identified as a malformation in the region of the cavernous and circular sinus and the other apparently connected through the great vein of Galen and the straight sinus to the right side of the posterior fossa subtentorially. The malformation was extensive and deep. The tentorial and infratentorial dural sinuses were greatly enlarged. The size of the lesion precluded operation.

On the day after admission the child had another convulsion with tonic-clonic movements of the left arm and leg both held in partial flexion. The seizure lasted about two

minutes. Subsequently the infant had repeated episodes of generalized twitchings, starting on the right with convulsions of the right arm and leg. Later a left hemiparesis was noted. weeks after admission. Extreme opisthotonus and high-pitched cry were noted. The infant died at the age of 4½ months, 12 weeks after admission.

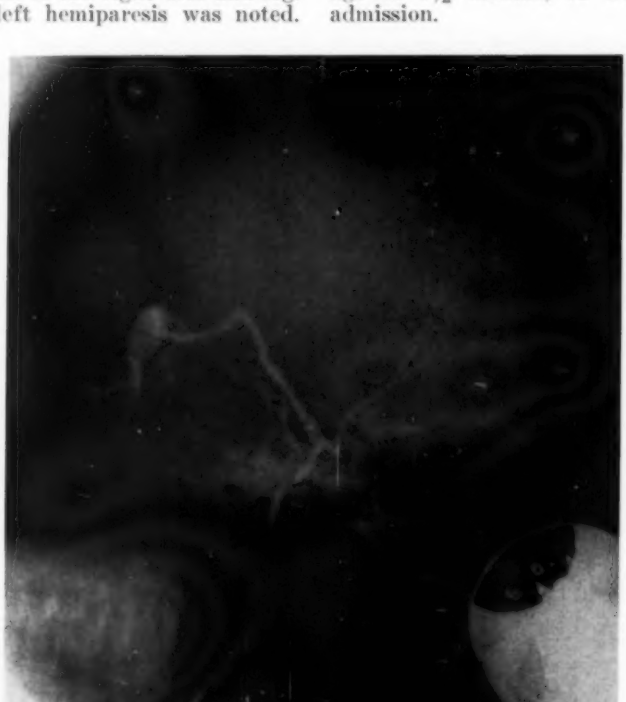

Fig. 1.

The head was constantly turned to the right side. Fundoscopic examination revealed a progressive right optic nerve atrophy. The course was steadily downward, with fever of 38.5° up to 39.2° C. without obvious signs of infection. However, during the last ten days before exitus the temperature was subnormal, even below 34° C. Pulse rate varied between 140 and 230, respirations between 40 to 96. The head circumference increased rapidly from 40.5 cm. on admission to 44.5 cm. at four weeks, 47 cm. at eight weeks, and 48 cm. at 12

Post-mortem examination was done by Dr. Samuel T. Nerenberg and the detailed studies of the brain were made by Dr. Knox Finley.* Only the brain will be described, as the rest revealed no pertinent pathology. The left cerebral hemisphere appeared about 20 to 25 per cent larger and somewhat paler than the right. The grayer right and smaller cerebral hemisphere had two large vessels extending from the approximate region

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of the falx down along what would appear to be the central fissure. It terminated in an ill-defined dark grayish area lying on the lateral portion of the frontal lobe, measuring approximately 3 cm. in diameter. The surface of this grayish area, which was firmer than the surrounding brain parenchyma, was striated by numerous tortuous vessels. The posterior two-thirds of the falx were much thicker and firmer than normal. Posteriorly to the region of the vein of Galen and at the point where the falx joins the tentorium, there was considerable thickening by a combination of a firm and fibrinous tissue between the two outer layers of the falx and the tentorium, becoming eventually a tumor mass greatly distending the terminal portion of the falx but primarily the tentorium. This tumor mass measured approximately 10 cm. in an anterior-posterior-inferior direction and 3 to 4.5 cm. in width. Running through or near the center of the tumor mass was a large channel, rather tortuous in its course, the lumen measuring 5 to 8 mm. in diameter. The brain stem was not unusual in the gross though there had been some distortion from the terminal hemorrhage of the above-described tumor and possibly in fixation. However, the subarachnoid spaces at the base of the brain stem, cerebellum, and, for that matter, part of the base of the cerebral hemispheres had a yellowish gold-brown discoloration. The right cerebellar hemisphere was slightly more than half the size of the left.

It was not possible from the very friable, distended, collapsed brain to find a vessel which communicated with the internal carotid or main cerebral vessels to the tumor mass in the posterior tentorium and falx. The large vessels over the central portion of the right cerebral hemisphere which had now been separated from its apparent connection with the tentorium did appear to have penetrated the falx about 1 to 2 cm. above and anterior to where the falx became continuous with the tentorium. On opening the temporal and occipital horn of the right ventricle there was a very rich and tortuous mass of subependymal vessels seemingly involving most of the subependymal region of these portions of the right lateral ventricle. On opening the anterior horn of the right lateral ventricle, the anomalous vascular structures could likewise be traced into this portion of the ventricle. These vessels were continuous with the 3 by 4 cm. grayish mass, with tortuous vessels described from surface observations of the lateral part of the right frontal lobe. Opening the ventricle of the left hemisphere showed a tremendous dilatation throughout, the overlying white matter and cortex measuring in thickness not more than 0.5 cm. plus-minus.

An attempt was made to find some direct channel between the circle of Willis and the proximal portions of the main cerebral vessels, that is, the anterior middle and posterior cerebral vessels, but, after fixation, no direct communication could be found. However, it should be pointed out that because of the great difficulties in removing such a brain with tremendous internal hydrocephalus, such communication could have been separated. Frontal sections through the brain stem and cerebellum revealed a tremendously dilated fourth ventricle. Sections of the spinal cord were normal at cervical, thoracic and lumbosacral levels.

Numerous sections were examined with the Nissl and hematoxylin and eosin stains. Sections from the falx show a conglomeration of vessels, most of which were of thick-walled (arterial) type. A number of the vessels were thrombosed. Hemosiderin pigment and mononuclear leukocytes were present throughout the sections. Many of the vessels contained calcification in their walls. Sections through the cortex showed the pia-arachnoid meninges to contain numerous anastomosing and calcified

thin-walled vessels; many of the lumina were thrombosed. The underlying cortex contained scattered small hemorrhages and collections of hemosiderin pigment. In a number of areas there was proliferation of the astrocytes and microglia. Sections through the cerebellum and pons showed marked deformity and flattening. Much of the cerebellar tissue was replaced by a vascular malformation made up of numerous, dilated, blood-filled and thin-walled spaces separated by parenchyma. Scattered gliosis and occasional hemorrhages were seen between the vessels. The cerebellum and cortex showed degenerative changes. Sections through the medulla showed collections of hemosiderin pigment on the surface. Sections through the spinal cord (cervical portion) showed a collection of mononuclear cells and hemosiderin pigment surrounding the meninges. Sections through the thoracic cord showed subdural hemorrhages, degenerating leukocytes and hemosiderin.

Diagnosis.—Extensive vascular malformation of the central nervous system (angiomatosis of meninges and brain). Subarachnoid and subdural hemorrhage recent and old.

DISCUSSION

Although cerebral vascular anomalies are congenital in origin, manifestations of their presence are seldom evident at birth. In this review, only one other was reported as young as our patient. One author notes that less than 10 per cent manifest themselves in the first decade. One child had convulsions starting at 4 months, another showed symptoms at 1 year, one was diagnosed at 2 years, one at 3 years, and another at 6 years. Curiously there is very little mention of associated visible clues. In our case the biopsy of the soft tumor mass virtually made the diagnosis. It was then confirmed and delineated by angiography and ventriculograms.

A pulsating exophthalmus was noted in one case and a cirsoid aneurysm of the scalp in another. In the majority of cases, diagnosis must be made on symptomatology and by angiography.

The presenting symptoms as gleaned from the review of the literature may be grouped as follows:

1. Palsies are often unilateral, the patient presenting with a hemiplegia which may involve both the motor and sensory areas and often shows progressive signs. Palsies of the cranial nerves have been noted, notably of the third, sixth, and eleventh. Optic atrophy occurs at times.

2. Convulsions or epileptic seizures are commonly recorded as a first sign of nervous system pathology. The attacks may be the Jacksonian type, or generalized. They may occur at long intervals or recur frequently. In some instances they date back to childhood.

3. Cerebral or subarachnoid hemorrhage at any time in life may be due to angiomas.

4. Mental deterioration is frequently noted and is usually progressive.

5. Psychopathic changes are not uncommon.

6. Progressive hydrocephalus occurs when spinal fluid flow is obstructed.

7. Subjective symptoms may be those associated with increased pressure, such as headache and vomiting. In addition, noises in the head may be a complaint.

8. Objective findings have been optic atrophy, nystagmus, bruits over

the head, exophthalmus, calcifications shown by plain x-ray, and occasionally outward signs such as hemangiomata or abnormal vascularity. The anomaly not infrequently is amenable to surgery. Extirpation of the mass may be possible; sometimes hemispherectomy is indicated. Occasionally ligation of vessels leading to the mass may give some relief. Ligation of the carotid artery is inadequate treatment. Radiation is of no value.

SUMMARY

The clinical history and autopsy findings are presented in a child with cerebral angiomatosis. The pertinent literature has been reviewed. General symptoms and signs of such lesions are paresis, epilepsy or convulsions, hemorrhage, less commonly chronic headache, mental deterioration, cranial bruits, visual field defects, diplopia due to sixth nerve paralysis, and symptoms secondary to increased intracranial pressure.

Final diagnosis usually can be made by intracranial angiography. The treatment of choice is radical surgical excision or obliteration and should be carried out whenever feasible. The value of intracranial arterial ligation or incomplete removal of the anomaly may be questioned. Radiation is of no value.

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MECONIUM PERITONITIS CAUSED BY A RUPTURE OF A MECKEL'S DIVERTICULUM IN A NEWBORN INFANT

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MECONIUM peritonitis results from the leakage of meconium into the peritoneal cavity. It is the consequence of the rupture of a portion of the gastrointestinal tract during the late intrauterine or early neonatal period and is a chemical and foreign-body peritonitis. Bacterial peritonitis does not occur until later, since the bacterial flora of the gastrointestinal tract is usually not established until after the first 24 hours of extrauterine life.

Meconium peritonitis is a relatively infrequent occurrence, as reported by the data of Bendel and Michel[1] who found only three cases in a series of 108,744 consecutive live births. The condition was first described by Siebold[2] in 1825 who reported a case of rupture of the stomach in a newborn infant. Simpson[3] later described the entity of meconium peritonitis in greater detail. Since that time, over 100 cases have been reported in the literature.[4] The most common etiological factors causing rupture of the bowel and resulting in meconium peritonitis have been listed as atresia of the bowel, volvulus, and meconium ileus. There have been two cases of ruptured Meckel's diverticulum reported in a newborn infant.[5, 6] However, in these two cases, symptoms and signs did not appear until after the third day of life. Potter[7] mentioned a case of an infant who presented the symptoms of shock and abdominal distention on the second day of life. Autopsy revealed that there were multiple perforations of the bowel and that two of these were close to a Meckel's diverticulum.

The purpose of the present case report is to describe an infant with meconium peritonitis apparently present at the time of delivery. Autopsy revealed that this was caused by the rupture of a Meckel's diverticulum. A review of the literature has failed to reveal a report of a case of meconium peritonitis caused by rupture of a Meckel's diverticulum occurring during intrauterine life.

CASE REPORT

The patient, a Latin American male infant, was born after 8½ months' gestation and was the product of the mother's eleventh pregnancy. The infant weighed 6 pounds and 2 ounces (2,693 grams). The only complication of pregnancy was that of polyhydramnios which was present during the last two months of gestation.

The delivery was complicated by the presence of a double loop of umbilical cord twisted around the neck. This was severed after delivery of the head. There was difficulty in delivering the body because of the marked abdominal distention of the infant. The skin of the abdomen presented a bluish discoloration associated with large ecchymoses. The child was limp, cyanotic,

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Fig. 1.

Fig. 2.

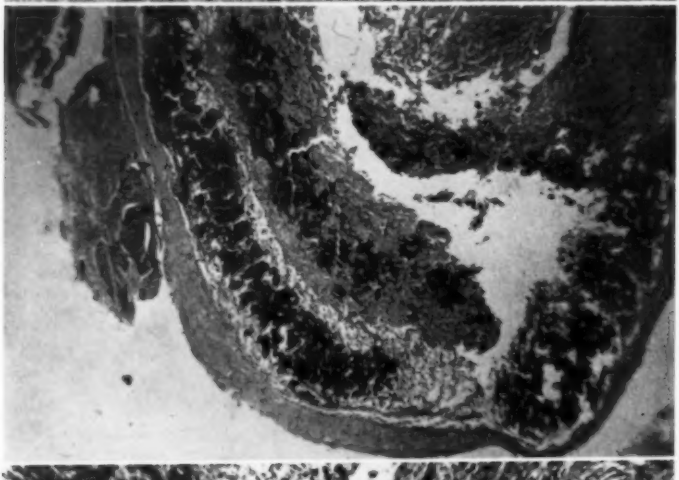

Fig. 3.

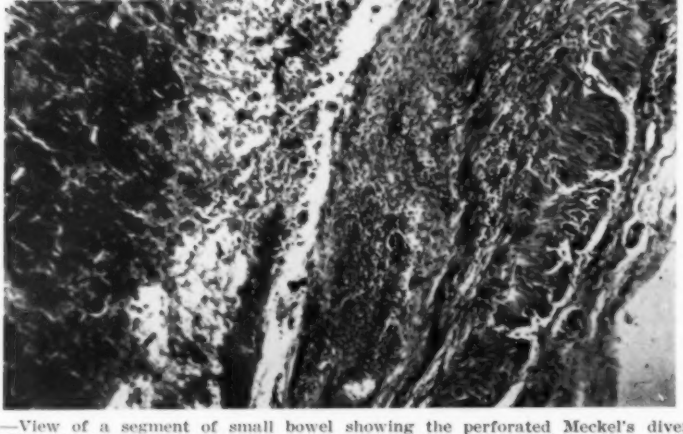

Fig. 1.—View of a segment of small bowel showing the perforated Meckel's diverticulum and the adjacent site of adherence of the ruptured tip of the diverticulum to the wall of the ileum.

Fig. 2.—Photomicrograph of a section of the distal end of the Meckel's diverticulum after separation from the point of attachment to the adjacent bowel wall. The calcific material is within the lumen. The attached fragment of muscle was pulled from the wall of the ileum during separation. (Hematoxylin and eosin, ×35.)

Fig. 3.—Photomicrograph of a section through the ileum adjacent to the Meckel's diverticulum showing extensive inflammatory reaction throughout the entire wall. (Hematoxylin and eosin, ×100.)

and apparently was in shock following delivery. The heart rate was noted to be 160 to 180 per minute. The child was placed in an incubator supplied with continuous oxygen after the administration of caffeine sodium benzoate. A tentative diagnosis of a ruptured viscus with meconium peritonitis was made, but the physical condition was such that surgical exploration could not be done. Death occurred six hours after birth.

AUTOPSY FINDINGS

There was edema of the scalp over the left parietal area and the face and eyelids had a swollen puffy appearance. The abdomen was found to be markedly distended and presented numerous petechiae as well as large ecchymoses of the skin. Circumference of the head was 32 cm., of the chest 30 cm., and of the abdomen 36.5 cm. Examination of the body cavities revealed atelectasis of both lungs with marked congestion. The heart presented no abnormalities. The abdomen was filled with approximately 150 c.c. of thick yellow-green fluid. The peritoneal surfaces were covered with yellow-green fibrous exudate, causing adherence of the loops of intestine. This exudate was present throughout the peritoneal cavity and covered all peritoneal surfaces. Dissection of the gastrointestinal tract revealed a ruptured Meckel's diverticulum 22 cm. proximal to the ileocecal valve (Fig. 1). The entire Meckel's diverticulum, and a 12 cm. segment of adjacent ileum was black-green and gangrenous. No other sites of rupture were identified. No other anomalies were demonstrated. The other organs were found to be of normal development and appearance.

A cephalhematoma was found in the left parietal area and a subdural hematoma demonstrated on the left.

The microscopic examination of the peritoneum-covered organs revealed changes characteristic of meconium peritonitis. There was abundant fibroblastic activity with fibrous proliferation associated with infiltration of histiocytes, fibrin, and calcific salt deposit. Sections taken through the perforated portion of the Meckel's diverticulum (Fig. 2) showed this area to be completely devoid of mucosa. The muscularis was found to be intact except at the point of rupture. The lumen showed an abundance of mucous material. The inner surface of the diverticulum showed calcific deposit as well as histiocytic infiltration and fibroblastic activity.

The remainder of the gastrointestinal tract presented an intact mucosa. The serosal surface throughout its entire length was covered with exudate of the meconium peritonitis (Fig. 3).

DISCUSSION

Boikan[8] states that the following criteria need to be established in the diagnosis of meconium peritonitis at autopsy: the presence in the peritoneal cavity of meconium, calcified meconium, mucous droplets, foreign-body giant cells, cells from the surface perforation, fibrinous or fibrous adhesions, and, rarely, lanugo hair. The calcified meconium is represented by many pinhead- to pea-sized yellowish lesions scattered through the peritoneal cavity and lightly adherent to the omentum. There may be larger patches having scattered calcareous nodules, and areas of fat necrosis.

Meconium is present in the intestine of a 3-month-old embryo.[9] It would, therefore, be theoretically possible for meconium peritonitis to occur any time after the first trimester of pregnancy. Intestinal peristalsis, however, which is probably necessary to cause rupture of the bowel, has not been observed prior to the fifth month of pregnancy. It would seem probable, then, that with the possible exception of trauma, meconium peritonitis cannot occur before the last half of gestation. Meconium is a mixture of cast-off epithelial cells, bile pigment, bile salts, cholesterol, fat,

stearic acid, sebaceous material from swallowed liquor amnii, mucin, and salts, to which pancreatic and gastric secretions and enzymes are added at about the fifth fetal month.[10]

Approximately 50 per cent of instances of meconium peritonitis are secondary to congenital malformations of the gastrointestinal tract.[8] These lesions cause intestinal obstruction, followed by gangrene and perforation.[8, 11] Malrotation, volvulus, atresia, mesenteric hernia, duplication, and diverticulum of the bowel are those lesions which have been most frequently implicated. Meconium peritonitis is not an uncommon sequel of meconium ileus. Trauma during delivery may occasionally play a role.[12] In many instances of meconium peritonitis there is no evidence of an obstruction; neither the etiology nor the actual site of perforation has been found at operation or autopsy in these cases.[8]

The symptoms and signs of meconium peritonitis are abdominal distention, persistent vomiting, and failure to pass a stool. The abdominal distention may be so marked as to interfere with delivery, as in the present case.

Roentgenologic examination of the abdomen reveals many irregular shadows of calcific density scattered throughout the peritoneal cavity, lying outside the loops of bowel, within the bowel lumen, or loosely adherent to the peritoneum. This x-ray appearance is pathognomonic of meconium peritonitis.[13]

There have been some instances of meconium peritonitis of unexplained etiology which have occurred in utero. The diagnosis in these cases has been made at autopsy or abdominal operation later in life for an entirely unrelated condition, when nodules of calcified meconium accompanied by dense bands of adhesions have been found.[14]

The present case represents an example of meconium peritonitis due to intrauterine rupture of a Meckel's diverticulum. The gross appearance of the site of perforation and adjacent bowel with widespread peritonitis indicates that the perforation occurred prior to delivery. The marked abdominal distention due to the free peritoneal fluid was sufficient to cause dystocia which resulted in trauma to the skin of the abdominal wall. It is postulated that an obstruction was present in the proximal portion of the Meckel's diverticulum, resulting in distention of the diverticulum and subsequent necrosis and perforation. Infarction of the wall due to arterial or venous thrombosis was not demonstrated, but this remains a possible cause. Infarction and necrosis due to torsion of a portion of the mesentery of the diverticulum could not be demonstrated.

The prognosis of infants with meconium peritonitis is extremely poor. However, there have been 18 infants reported who have survived surgery.[15] The diagnosis must be made early and immediate abdominal exploration should be performed. The site of obstruction and perforation can then be identified and corrected. Only when prompt diagnosis is made with immediate surgical intervention can survival of infants with meconium peritonitis be anticipated.

SUMMARY

1. A case of meconium peritonitis due to a ruptured Meckel's diverticulum is presented. It is believed that perforation occurred in utero.

2. A brief review of the clinical and autopsy findings of meconium peritonitis is made.

3. The mortality is extremely high. Prompt diagnosis and immediate surgical exploration offer the only chance of survival for these infants.

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MULTIPLE HEPATIC ABSCESSES DUE TO ASCARIS LUMBRICOIDES

Case Report

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ASCARIASIS is world-wide in distribution and is regarded by some authorities as perhaps the most common parasitic infestation in man.[1, 3, 7] It is therefore to be suspected that complications should be reported in association with ascaris parasitism; indeed, the surprising fact is that more complications have not been reported.

Ectopic migration of the ascaris is usually associated with fever or the administration of anthelmintic medication. Migration of this parasite into the lumen of the appendix, bile ducts, pancreatic duct, and through freshly sutured wounds has been reported.

CASE REPORT

C. J. R., a 2½-year-old Negro girl, was seen at Hermann Hospital for the first time on Oct. 18, 1957, with the chief complaints of severe constant abdominal pain, persistent anorexia, and increasing lethargy. The illness dated from one month prior to admission at which time she had mild cramping abdominal pain, low-grade fever, and weight loss of 10 pounds in one month. Some two weeks prior to admission, the mother noted several round, elongated worms (3 to 4 inches in length) in the stool, and administered a patent worm medication containing gentian violet. The child had been seen to eat dirt on at least one occasion.

The past history was noncontributory except that the child had varicella at the age of 14 months and rubeola at 20 months. Immunizations included 4 injections of diphtheria, pertussis, and tetanus antigen, two polio inoculations, and two typhoid injections.

The family history revealed that others of the five siblings were also infested with roundworms. The family lived on a small farm and drank untreated well water and raw milk. An indoor flush-type toilet and septic tank had only recently replaced an outdoor privy.

Physical examination on admission revealed the following: temperature 103° F. (39.6° C.) rectally, pulse 124 per minute, respiration 44 per minute, blood pressure 98/74. The child appeared chronically ill and was in acute distress. Weight on admission was 26 pounds (11.8 Kg). The essential findings were a loss of subcutaneous fat, protuberant abdomen and absent bowel sounds. Blood studies revealed hemoglobin 10.4 Gm. per cent, hematocrit 34 per cent, white blood cells 23,900, eosinophils 33 per cent, polymorphonuclear neutrophils 32 per cent, lymphocytes 30 per cent, and monocytes 5 per cent. Stool examination revealed the presence of adult *Ascaris lumbricoides* worms and ascaris ova.

The initial impression was ascaris infestation with possible intestinal perforation and peritonitis. Roentgenograms, however, revealed no free

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air in the peritoneal cavity, and further examination failed to confirm the clinical impression.

Treatment consisted of chloramphenicol (125 mg. every 6 hours) initially, to which diethylearbamyl piperazine (120 mg. three times a day) was added on the third hospital day. Piperazine citrate (1.25 Gm. daily) was substituted for the diethylearbamyl piperazine on the sixth hospital day.

The abdominal distention decreased and the child appeared improved clinically. However, she continued to have a low-grade fever up to 102° F. (39° C.). On the seventh hospital day, a mass, thought to be liver, was palpated 4 cm. below the right costal margin. The mass gradually enlarged until, on the seventeenth hospital day, its lower edge could be palpated in the right upper quadrant 8 cm. below the costal margin. The mass was tender and firm. The mass was still present on the twenty-fifth hospital day, and at this time a separate nodular mass approximately 5 cm. in diameter was palpable in the left upper quadrant. Surgical consultation was obtained, and an exploratory laparotomy was performed on the twenty-sixth hospital day. At the time of operation both lobes of the liver were found to be enlarged and contained multiple yellowish-gray, indurated nodules varying in size from 1 to 3 cm. in diameter (thirteen nodules were delineated). One of these nodules was excised in toto. There was lymphadenopathy about the porta hepatis, superior mesenteric artery, and left renal vessels.

Postoperatively the child continued to have fever ranging up to 104° F. (40° C.) until, on the fifth postoperative day, a wound abscess was noted and drained. Culture of the purulent material from the abscess revealed *Aerobacter aerogenes*. After drainage of the wound abscess, the fever subsided, and subsequently her course was uncomplicated. The general nutritional status gradually improved. Weight at the time of discharge was 27 pounds (12.2 Kg).

Liver function studies at the time of admission revealed the total serum protein was 5.9 Gm. per cent, albumin 3.4 Gm. per cent, globulin 2.5 Gm. per cent, bilirubin 0.9 mg. per cent, thymol turbidity 2.4 units, and cephalin flocculation negative at 48 hours. Prior to laparotomy, the total serum protein was 7.0 Gm. per cent, albumin 3.6 Gm. per cent, globulin 3.4 Gm. per cent. One week after laparotomy, the bilirubin was 0.2 mg. per cent, thymol turbidity 5 units, alkaline phosphatase 23.4 Bodansky units, and a Bromsulphalein study showed retention of 4.5 per cent at one hour. Three weeks postoperatively, the total serum protein was 7.1 Gm. per cent, albumin 4.5 Gm. per cent, globulin 2.6 Gm. per cent, bilirubin 0.6 mg. per cent, alkaline phosphatase 15.5 Bodansky units, thymol turbidity 2.4 units, and cephalin flocculation 1 plus at 48 hours. The child had four stool examinations negative for ova and parasites prior to discharge.

Pathological examination of the liver biopsy was reported as follows: "The specimen consists of two pyramidal-shaped fragments of yellow liver tissue. The fragments measure $2 \times 1.5 \times 2$ cm. each. On each fragment at 0.7 cm. from the capsular surface there is a portion of an abscess cavity. The cavity is irregular in shape and the walls are yellow and shaggy. Surrounding this area is a margin of firm white tissue, 0.5 cm. in thickness. Microscopically the sections of liver tissue exhibit fairly large abscess cavities replacing liver tissue. These cavities are lined by granulation tissue covered over the inner aspect by some necrotic and degenerating polymorphonuclear exudate and cellular detritus. Embedded in this exudate are numerous ascaris ova. These ova reveal the organized nucleus and heavy cell wall typical of the fertilized egg. Some ova possess and some lack the albuminous covering. One of these abscess cavities also contains a portion of the parasite. Adjacent liver tissue shows a profuse eosinophilic

Fig. 1.—Section of liver tissue containing abscess, showing the cuticle of an adult ascaris worm. (Hematoxylin and eosin, ×30; reduced ¾.)

Fig. 2.—Enlarged portion of Fig. 1 showing detail of ova, cuticle, and cellular detritus. (Hematoxylin and eosin, ×300; reduced ½.)

leukocytic, histiocytic and plasma cell infiltration with some fibrosis. More distant portions of the liver show irregular fairly wide bands of similar fibrocollagenous tissue supporting medium-sized slightly proliferating bile ducts. Pathological Diagnosis: Biopsy specimens of liver: hepatic abscesses due to parasites and ova, Ascaris."

Further study of the microscopic sections with a parasitologist revealed that only the most resistant portions of the adult ascaris remained, namely the cuticle and eggs. The cellular debris in the lumen of the cuticle was smaller than the surrounding liver tissue and was thought to be cells from the worm itself. In view of these findings it was felt that the worm was not viable and was undergoing degeneration. Therefore, it was further felt that any remaining adults in the liver tissue would undergo similar degeneration and the infestation of the liver tissue would eventually subside spontaneously without any treatment being directed at these ectopic parasites.

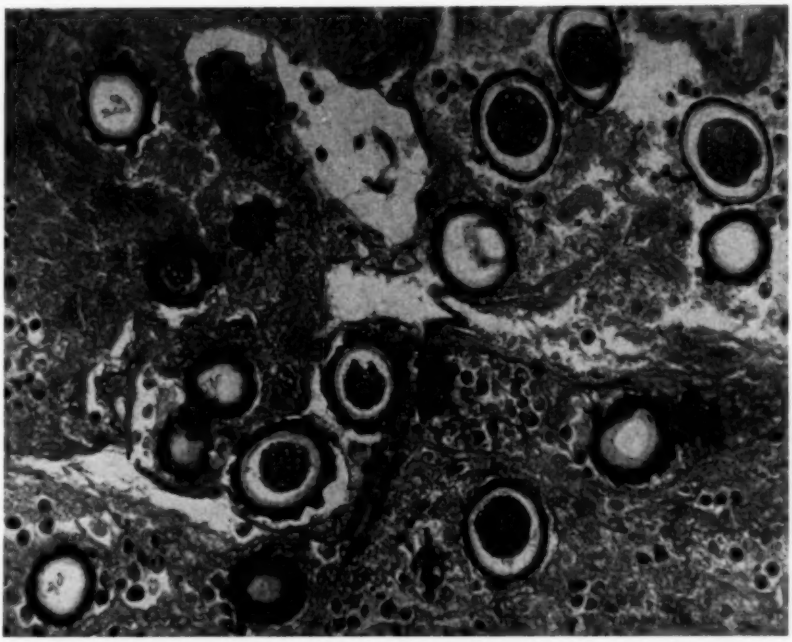

Fig. 3.—Section of liver tissue showing various stages of maturation of ascaris ova. (Hematoxylin and eosin ×600; reduced ½.)

DISCUSSION AND REVIEW OF THE LITERATURE

The normal habitat of the ascaris worm in man is in the small intestine, primarily the jejuneum; however, the worms tend to migrate when they are disturbed, especially when the host has high fever and when anthelmintics are administered. Several reports of cases of liver abscess associated with ascariasis have appeared,[6, 11, 12, 13, 15, 16, 17] the largest series being reported by Crowell[6] in 1920 (seven cases) and by Henao[17] in 1957 (seven cases). The hepatic abscesses appear to be due to migration of the ascaris worms into the bile

ducts, gradually reaching the smaller biliary radicals, ovipositing and stimulating foreign body reaction along the route. Whether each abscess is due to an individual parasite or whether several abscesses are due to the same worm cannot be determined in this case since only one abscess was actually biopsied.

The signs and symptoms of this disease are as follows: vague abdominal complaints, vomiting, passing worms per rectum, vomiting worms, and low-grade fever.[12] The only physical finding that is noted with any consistency is abdominal protuberance,[12] and the most constant laboratory finding is recovery of ova in the stool.

At present, piperazine is the treatment of choice, and excellent results are obtained. The mode of action of this drug is upon the musculature of the parasite, causing paralysis and hence interfering with or preventing migration. In this particular case, it is the consensus that migration probably occurred at the time when treatment had been undertaken with gentian violet.

Our plan of therapy consisted of treatment with piperazine citrate (100 mg. per kilogram) until the stool was cleared of ascaris ova, re-examination of the stool at monthly intervals, and retreatment if the ova reappeared. In addition, all members of the family were treated with piperazine. Reinfestation from the home environment, particularly the dooryard, which is most likely to be thoroughly seeded with ascaris ova, presents a real problem. However, the probability of reinfestation is less since the installation of a flush toilet in the house.

SUMMARY

A case of ascaris infestation complicated by multiple hepatic abscesses is presented. In one of the abscesses fertilized ova and a portion of the parasite were demonstrated by biopsy. It is felt that the abscesses in the liver were due to the migration of the adult worm through the biliary radicals, and that the migration was associated with the administration of gentian violet. A plan of therapy is presented. This case represents a serious and infrequent complication of a common condition encountered in pediatric practice, and shows that ascariasis cannot be considered an entirely benign condition.

I wish to express my appreciation to R. J. Blattner, M.D., W. G. Brown, M.D., and F. Connell, Ph.D., for their helpful suggestions in the preparation of this manuscript.

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Homœopathic Vaccination

A medical friend has recently mentioned to me an homœopathic practise, which as it illustrates the little value of the Compulsory Vaccination Act, deserves public notice.

On reminding one of his patients that the time has arrived for the vaccination of her infant, she replied that this was no longer necessary for that an homœopath, under whose care her family had been placed whilst she resided in London, had sent her a powder, which would answer the same purpose. To convince her medical attendant of the truth of her assertion, she gravely showed him a pimple on the nates, which had followed the administration of the medicine.

My friend remained incredulous; and to test the value of this homœopathic discovery, the child was vaccinated. The vesicles ran their usual course, and the parents were so far convinced, that they allowed their two elder children to be vaccinated, and with the same result.

I need only add, that the homœopath had filled in one of the ordinary certificates for transmission to the registrar without ever seeing the child.

British Medical Journal
July 19, 1858

CICATRICIAL STENOSIS OF THE ESOPHAGUS FOLLOWING INGESTION OF A SINGLE URINE-SUGAR REAGENT TABLET

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RECENTLY Canby[1] called attention to the hazard of esophageal stricture from the ingestion of Clinitest urine-sugar reagent tablets.† He stated that there were no previous reports in the literature and that the manufacturer was unaware of similar occurrences. Personal observations suggest that these accidents may not be rare, though infrequently reported.

We wish to report a case of complete esophageal obstruction which resulted from the ingestion of a single Clinitest tablet. The nature of the trauma is discussed, with suggestions for improved management.

CASE REPORT

A 5-year-old white girl was seen in the Dispensary, Fort Lewis, Washington, on May 9, 1956, with the complaint that she had ingested a single Clinitest tablet. The tablet was obtained from a bottle kept in the bathroom medicine cabinet by the grandmother, a diabetic who was visiting in the home. Following ingestion of the tablet, the patient had vomited promptly. She had no complaints when seen. Gastric lavage was carried out with clear return from the stomach. Diagnosis was recorded as "copper sulfate ingestion" and she was released for observation at home.

That same night the patient returned with complaints of burning in the throat and epigastrium. Physical examination was negative. Bland fluids, an antacid and antispasmodic were prescribed.

She was next seen on May 24, 1956, with complaints of persistent vomiting since the previous visit and weight loss. Part of any food she attempted to eat was regurgitated. An esophagram and upper gastrointestinal x-ray study were ordered. These were performed May 28, and reported as showing no abnormality (Fig. 1). However, when next seen a few days later, on June 1, she was unable to swallow any solids, and weight loss had progressed to an alarming degree. Hospitalization was arranged and she was admitted to Madigan Army Hospital, June 4, 1956.

On admission she was alert, friendly, and cooperative. She complained of hunger, but not of pain. She refused solid foods and chose only liquids. When coaxed to take something solid, she would swallow it and promptly regurgitate it violently. She was observed to chew her meat, swallow the juice and spit out the rest. She filled her emesis basin with frequent expectoration of viscid saliva.

Emaciation was well advanced. Her weight on May 9, 1956, had been 43 pounds. On admission it was 33 pounds. Height was 43½ inches. Pulse, temperature, and respiration were within normal limits. Physical examination was not remarkable except for evidence of weight loss, poor skin elasticity, and dull, lifeless hair.

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†Clinitest urine-sugar reagent tablets manufactured by Ames Co., Elkhart, Ind.

Laboratory studies revealed: urine—yellow, cloudy, acid, 1.016 specific gravity, albumin negative, sugar negative, 1 to 3 white blood cells; white blood count—19,200, with 30 per cent neutrophils, 68 per cent lymphocytes, and 2 per cent eosinophils; hemoglobin—13.0 Gm., hematocrit 39, and blood urea nitrogen 27 mg. per cent.

Clear liquids were prescribed, and on this regimen she was barely able to meet her fluid requirements while falling far short of caloric needs.

Repeat barium swallow on June 8 showed an almost complete obstruction of the esophagus 2 inches above the diaphragm (Fig. 2). (Retrospectively, this area demonstrated ulceration on the previous x-ray which had been interpreted as normal.)

The tube did not pass the obstruction on insertion and when taped in place the child would manage to pull it out. Even a thread could not be inveigled to pass. She had become very emotional and at times her speech seemed incoherent.

On June 13 the patient's weight was 29 pounds. She became unable to swallow even water. Intravenous fluids were begun and she was scheduled for surgery. After 24 hours' preoperative hydration, on June 14 a Witzel type gastrostomy was performed under general anesthesia. The patient withstood the procedure well, and feeding through the gastrostomy tube was begun the next day. This was rapidly advanced from clear fluids, to milk formula, to a diet of blenderized

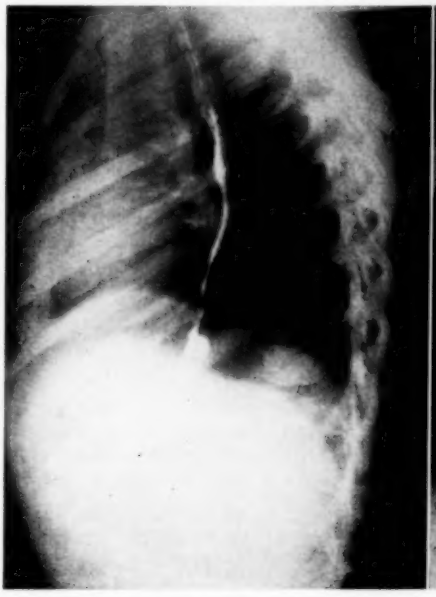

Fig. 1.

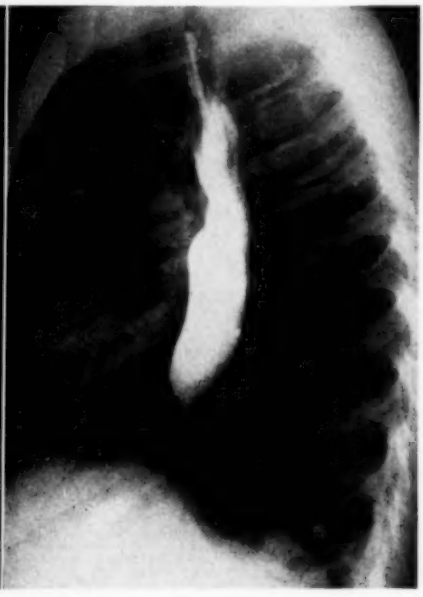

Fig. 2.

Fig. 1.—Esophagram of May 28, 1956. Originally interpreted as negative. An area of ulceration is demonstrated 2 inches above the diaphragm, but there is no obstruction.

Fig. 2.—Esophagram of June 8, 1956. An almost complete obstruction is present 2 inches above the diaphragm with dilatation of the proximal esophagus.

By June 11, weight had dropped to 30½ pounds, and attempts at intubation with a fine caliber polyethylene tube had met with successive failures.

solids. The patient became active and cheerful. She gained weight to 32 pounds by June 21, when she was discharged. She was not attempting any

oral intake and was still expectorating her saliva.

At home she was given blenderized food every three hours during the day and made steady progress marred only by an episode of tonsillitis which caused her to lose weight temporarily. After accidentally pulling out her tube on July 22, 1956, she was readmitted to Madigan Army Hospital.

Fig. 3.—Esophagram of May 16, 1957. Unimpeded passage of barium through a pliable, distensible esophagus is demonstrated. The operative site is recognizable as a minor irregularity 2 inches above the diaphragm.

Her weight on readmission was 35½ pounds. Physical examination revealed improved nutritional status, poor oral hygiene, and the abdominal scars of the gastrostomy. A No. 12 French catheter was inserted through the gastrostomy. Tube feeding was resumed and preparations for definitive surgery were begun.

Since there had been no improvement in ability to swallow and there was doubt if a lumen existed through the strictured area, esophageal resection was proposed. The nature of the trauma suggested that the esophageal lesion might be limited in extent. Esophagrams seemed to confirm this. A successful resection and end-to-end anastomosis offered immediate relief and the attractive possibility of freeing the patient from years of unpleasant and hazardous bougienage.

On Aug. 6, 1956, left thoracotomy was performed through the eighth interspace, centering the incision over the posterior axillary line. The esophagus was dissected free near the diaphragm and the stricture palpated 1½ to 2 inches above the cardia of the stomach. The obstructed segment measured ½ inch in length and involved only mucosa. There was no involvement of the muscular layers or attachment to surrounding tissues. A

circumferential incision was made through the musculature and the strictured area of mucosa was dissected free and sent to the pathologist. End-to-end anastomosis of the mucosal and muscular layers was accomplished without difficulty, using two rows of interrupted silk sutures. Parietal pleura was placed over the anastomosis and a catheter installed leading from the left diaphragm to a water-seal drainage.

Surgery was well tolerated. In the immediate postoperative period, hydration was maintained by intravenous infusions. Nothing was given by gastrostomy for fear of reflux up the esophagus. When chest x-ray was clear on August 8, the drain was removed.

On August 11 cautious feedings per gastrostomy tube were successful. The following day the child took and retained fluids by mouth. There was no pain or difficulty in swallowing. The gastrostomy tube was clamped off and a regimen of soft solids and blenderized foods progressing to a regular diet begun. On August 13 she was discharged.

Subsequently, the child resumed a normal diet. The gastrostomy tube was removed and the fistula promptly closed. Barium swallows performed Aug. 22, 1956, and May 16, 1957, revealed rapid passage of the contrast medium into the stomach. The esophagus appeared distensible throughout, but a slight narrowing could be seen at the site of anastomosis (Fig. 3). Her general health continued excellent and there were no complaints referable to the chest, abdomen, or esophagus when last seen on March 10, 1958, two years after her original injury.

PATHOLOGIC DESCRIPTION

The specimen consisted of a 1.4 by 1.0 by 0.8 cm. roughly cylindrical piece of firm pink tissue with irregular outer margins. Each end was covered by pink, glistening mucosa showing a central dimple 2 to 4 mm. in width. Cross sections revealed a fibrous central area, and no lumen was apparent to the naked eye (Figs. 4 and 5).

Fig. 4.

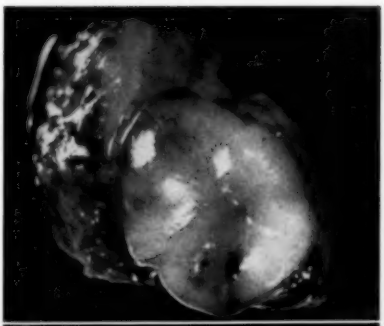

Fig. 5.

Figs. 4 and 5.—End and side views of the small segment of resected esophagus. No lumen could be demonstrated through the tissue in the gross specimen.

Microscopic sections revealed the esophageal lumen to be patent, but reduced to less than 1.0 mm. in diameter in the mid-portion of the specimen. The bordering squamous epithelium was well preserved. Extensive fibrosis of the mucosa, submucosa and, to a lesser degree, of the muscularis was present. There was patchy perivascular lymphocytic and plasmacytic infiltration (Fig. 6).

DISCUSSION

The Nature of the Trauma.—The Clinitest tablet contains sodium hydroxide, sodium bicarbonate, citric acid, and copper sulfate. When dropped into water, the tablet produces an initially acid pH which changes to strongly alkaline in a few moments (10 ml. of 0.2 N HCl was required to neutralize the alkalinity of 1 dissolved Clinitest tablet in our laboratory). The solution bubbles, evolving CO_2 gas, and as the sodium hydroxide dissolves the solution becomes hot. Depending upon the volume of the solution, the temperature will be raised very little or to the boiling point of water. The entire reaction is completed within 10 seconds.

Part of what transpires when such a tablet is ingested can be visualized by placing the tablet in the moistened palm of the hand. There is an interval of several seconds before the fizzing tablet becomes too hot to hold.

It seems that the tablet could traverse the esophagus without producing significant damage if the passage were rapid enough or if there were sufficient diluting fluid. The gas evolved through the interaction of the citric acid and sodium bicarbonate might also serve as a protective cushion. Once the tablet reaches the stomach its activity would be neutralized by gastric hydrochloric acid, mucin, and food contents. If, however, the tablet were arrested in its passage, a severe chemical and thermal burn would result from the action of the sodium hydroxide. This would be rather sharply localized with some involvement above and below the level of arrest, depending upon a host of factors.

Fig. 6.—Low-power microscopic view of transverse section of resected esophageal stenosis. The inflammatory and fibrotic reaction in the subepithelial layers is prominent. The lumen appears enlarged because of shrinkage during tissue fixation.

Thus the esophageal lesion produced by an ingested Clinitest tablet has certain features in common with other lye strictures, but appears more likely to result in a well-localized lesion. This was true of Canby's two cases.[1] Such strictures are amenable to cure by esophageal resection, the advantages of which, compared to a lifetime of bougienage, are worth serious consideration.

Other Observations.—Since Clinitest tablets have been in common use for many years now, it is surprising that esophageal lesions from their ingestion have not been more frequently noted. Owens[2] reported three cases of Clinitest ingestion in adults, only one of which resulted in stricture. Finestone[3] has informed us of an unreported case in his experience of a young woman who developed esophageal stricture after swallowing Clinitest tablets in a suicide attempt.

That the tablets may be ingested without harm under some circumstances is apparent from another instance supplied by Jankowich.[4] An elderly immigrant man was seen for diabetes mellitus at a Boston hospital. Clinitest tablets were supplied with verbal instructions for testing the urine four times a day. The patient returned several weeks later with complaints of gastritis. He had been taking one tablet orally four times a day! Fortunately, he had swallowed a large glass of water with each tablet. Follow-up examinations failed to demonstrate any permanent esophageal or gastric disorder.

Therapeutic Approaches.—There is a deceptive latent period between ingestion of a caustic and the onset of obstructive esophageal symptoms. The present case illustrates this well. Classical treatment has consisted of passing a string into the stomach during this period. This preserves the lumen as the esophagus constricts and the string is later used as a guide for the passage of bougies. Bougienage under direct vision through the esophagoscope and retrograde dilation through a gastrostomy are two other methods which have been used. All three methods of treatment are arduous, hazardous, partially disabling, and unpleasant for both patient and physician.

Relatively few lye strictures will lend themselves to simple esophageal resection with end-to-end anastomosis. That strictures produced by ingested Clinitest tablets may fall into this category is a significant observation. Where more extensive damage to the esophagus has occurred, resection and substitution of a bowel segment or a skin tunnel as reported by several authors will be required.[5, 6]

A recent report by Ray and Morgan[7] offers hope of a simpler, less excruciating approach. Eleven patients who had ingested lye were treated with cortisone and antibiotics. Only one patient of the eleven developed stricture. This is very encouraging, for in untreated cases followed up to two years after ingestion of lye, 25 to 50 per cent of the patients may be expected to develop strictures.

It is thought that the cortisone inhibits fibroplasia, permitting healing without deep scarring. Antibiotics control the inevitable infection which occurs in such lesions and thus further inhibit scarring, at the same time preventing the serious complication of infectious spread to the mediastinum. The important thing, apparently, is to

begin therapy immediately after the trauma. Cortisone must be given within the first 24 to 48 hours following injury if it is to suppress effectively the inflammatory response.[8] While the series reported by Ray and Morgan is too small and the follow-up too short to be conclusive, there is now an optimistic new direction open for investigation and therapy.

Prevention.—While there is a paucity of literature on the subject of Clinitest tablet ingestion, there are likely many unreported instances. There are over 1,000,000 known diabetics in the United States today, many of whom test their urine regularly with urine-sugar reagent tablets. The hazard of tablet ingestion by a small child is as ubiquitous as diabetes itself.

Recognition that these tablets can cause serious harm should lead physicians to prescribe caution in their use when they provide them to diabetic patients. They should be kept out of children's reach with the same care as other forms of lye. The 100 tablet prescription bottle of Clinitest is labeled "POISON" in red letters ⅛ inch tall. The manufacturer can scarcely be expected to be more explicit. However, such labels fail to command the same respect in the home as in the laboratory. Safer, nontoxic materials might be prescribed for urine sugar testing in the home. A number of such tests are now on the market.

SUMMARY

1. A case of esophageal stricture in a 5-year-old child which resulted from ingestion of a single Clinitest urine-sugar reagent tablet is presented. Successful treatment by esophageal resection and end-to-end anastomosis is described.

2. The nature of the trauma is examined and correlated with clinical, roentgenographic, and pathologic findings.

3. Suggestions for prevention and treatment of future cases are developed.

Photographs by Medical Illustration Section, Madigan Army Hospital.

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Clinical Pathological Conference

THE CHILDREN'S MEDICAL CENTER
BOSTON, MASS.

SIDNEY FARBER, EDITOR
JOHN M. CRAIG, ASSISTANT EDITOR

THIS patient was well until the age of 2 6/12 years, when he first began to have recurrent attacks of pallor, limpness, and loss of consciousness. Six of these attacks occurred; they were followed by drowsiness. At the age of 3 2/12 years he became pale and fatigued on exertion and then increasingly listless and anorectic. He held his hands across his chest when going upstairs and was believed by his mother to have become cyanotic. Nosebleeds had occurred three to four times over the month prior to admission. No mention of any heart abnormality had been noted on any of the many previous physical examinations.

The past history revealed that the child had eczema until 12 months of age. The family history showed that the maternal grandmother had pernicious anemia and rheumatic heart disease; two maternal aunts had anemia, and one of them had rheumatic fever as well.

At the time of admission, the vital signs were: temperature 97.2° F., pulse 144, and respirations 32 per minute; blood pressure, systolic 106 and diastolic 50 mm. Hg. The child was in the 50th percentile for height and weight, yet well developed. He was pale, thin, and listless, moving slowly and resting frequently. His neck had a prominent venous pulsation. The chest had an increased anteroposterior diameter, with a bulge in the precordial region. The heart was enlarged to percussion. On auscultation, a presystolic gallop, a Grade 3 apical systolic murmur, a loud pulmonary first sound, and a very loud pulmonary second sound were heard, followed by a short early diastolic murmur. No other abnormalities were found on physical examination.

The admission laboratory findings included a hemoglobin of 10.5 Gm. per cent, hematocrit 35 per cent, erythrocytes 3.81 million, leukocytes 9.4, and platelets 63 thousand per cubic millimeter. The differential leukocyte count was polymorphonuclear cells 58, basophils 5, lymphocytes 34, and monocytes 3 per cent. The erythrocytes were microcytic and hypochromic on smear. The reticulocytes were 2.4 per cent of the total erythrocytes. The sedimentation rate was 11 mm. per hour. The Coombs test for coating antibodies and the Hinton reaction were negative. The bleeding time was 17½ and the clotting time 6 minutes, with good clot retraction. A blood

sugar level during a syncopal attack was 240 mg. per cent. The electrocardiogram showed a pattern of right ventricular hypertrophy and P-pulmonale.

Roentgenographic studies revealed bilateral cardiac enlargement, normal-sized auricles, a small aorta in normal position, and a gross increase in the size of the main pulmonary arterial trunks and of the hilar vessels in the medial one-third of the lung. In the periphery of the lung the vessels were not prominent. The electroencephalogram was considered normal.

In the hospital the child was noted to have a very small exercise tolerance. In order to elucidate the nature of the anemia, a bone marrow under local anesthesia was done. Following this procedure, the child became limp, incontinent, and unresponsive. Resuscitative attempts were carried out, but with no success, and the child died on the second hospital day.

DR. WALTER T. GOODALE.*—This child's admission was promped by syncope, weakness, and pallor. Syncope has many possible etiologies, as pointed out by Dr. Soma Weiss,[1] who emphasized the importance, in most, of too small a flow of blood to the brain. He called attention to the syncope associated with pressure on the carotid sinus in which there was, first, an accompanying bradycardia and low pressure, or, second, low blood pressure alone, or, third, in some cases syncope with no demonstrable cardiovascular reflex, but suggesting some direct reflex to the brain. Though not pertinent to this case, the carotid sinus reflexes must always be considered in cases of syncope.

*Dr. Walter T. Goodale is Associate Cardiologist, The Children's Hospital, and Clinical Associate in Medicine, The Harvard Medical School.

From a circulatory point of view, syncope has two distinct categories of origin. In the first of these, there is a sudden fall in cardiac output secondary to bradycardia, or cardiac standstill—perhaps as the result of coronary thrombosis. The second general mechanism is a diminished diastolic filling of the heart chambers. If the return to either side of the heart is diminished, no blood will be available in the ventricles for the next cardiac systolic ejection. Such a change occurs, even one or two beats after the onset of a diminished venous return, because the blood remaining in the heart after systole is a relatively small fraction of the total volume of the heart chamber. If the ventricle fills to only one-half the total volume in each cycle, almost immediately the ventricle's output will be markedly reduced. Thus the hypotensive syncope of Dr. Weiss, not associated with bradycardia, may result from peripheral vasodilatation. Yet peripheral vasodilatation alone is not sufficient, since with a reduced systemic resistance secondary to a peripheral vasodilatation an increase in cardiac output will result. This peripheral vasodilatation must be sudden and abrupt to effect a sudden diminution in venous return.

In the present case, the history of pallor and weakness, between the episodes of syncope, suggests that there is a peripheral vasoconstriction in the extremities to maintain an adequate blood flow in the vital organs, in face of a probable, constant diminution in cardiac output. The fact that the syncopal attacks preceded an intensification of the pallor suggests that a sudden "triggering" reflex mechanism was the initiating factor of the sudden fall in cardiac output, rather than that

there was a primary failure in peripheral venous return.

The long interval between attacks and the negative electroencephalogram would tend to rule out a primary cerebral etiology for his fainting spells.

The child held his hands over his chest while going upstairs; this suggests that he was having chest pain.

The statement that he was blue on exertion is not as helpful as it might be. If a patient becomes blue when he is hot and exerting himself, or when he is in a hot tub bath, when nearly arterial blood is running close to the skin surface, it suggests that unoxygenated blood is passing into the arterial circuit. If he is merely blue when he is cold, this is a peripheral cyanosis, which does not always imply the presence of right-to-left shunt.

This child was thin. The pyknic build of such children has been related to their chronically low cardiac output from birth on, which is most characteristic of patients with atrial septal defects. These relationships, I think, are often overemphasized.

The venous pulsations in the neck were probably A waves due to a hyperactive atrial contraction, especially since there was a prominent P wave in the electrocardiogram, and a presystolic gallop—both findings consistent with this interpretation.

Prominence of the right side of the chest suggests a hypertrophy of the right ventricle from an early age. Enlargement of the left ventricle does not cause precordial enlargement because it enlarges posteriorly and laterally. The type of cardiac impulse is important because even at this age, if there is an actual forward motion of the lower left sternal border, or, if a "locking impulse" is present, one may strongly suspect left ventricular hypertrophy.

The presystolic murmur, if it were truly presystolic and not a split first sound, is almost surely an auricular sound. There was a loud mitral first sound and the pulmonic second sound was very loud; it was followed by a short diastolic murmur. These all are consistent with pulmonary hypertension and pulmonary insufficiency associated with that pulmonary hypertension. It would be important to know whether the apical systolic murmur was transmitted or whether it produced a thrill. The fact that it is best heard at the apex is not disturbing, for it could originate in one of four places. Such a murmur could be related to a ventricular septal defect, especially if the murmur was quite localized and there was no transmission. It could arise in a tricuspid insufficiency, or possibly a mitral insufficiency. It could arise, finally, in an infundibular stenosis of the pulmonary outflow tract, but this seems unlikely in view of the other findings. Many systolic murmurs in this area have no exact pathology, as in systemic hypertension. Of these possibilities, the two most likely are a ventricular septal defect, or nothing.

The blood data tell us, without further investigation, that the patient had an iron-deficient anemia. The electrocardiogram confirms the impression obtained from the physical examination—that of right ventricular hypertrophy due to an increase in work.

The roentgenographic studies showed a right and left ventricular hypertrophy. It is difficult to tell by x-ray whether the left ventricle is truly enlarged or merely displaced by an enlarged right ventricle.

Dr. Neuhauser, would you like to comment on this?

DR. EDWARD D. B. NEUHAUSER.—We saw this patient's chest films on two occasions. On the first, the right ventricle was definitely thought to be enlarged and the left was probably enlarged as well. The second is quoted in the protocol. The impression was that of a pulmonary hypertension but definite involvement of the left ventricle could not be determined.

DR. GOODALE.—If you suspect, Dr. Neuhauser, that the left ventricle is enlarged, you must have another lesion than pure pulmonary hypertension.

DR. NEUHAUSER.—We would agree to that. We are well aware of the difficulties in interpreting the size of the left ventricle.

DR. GOODALE.—Occasionally, in a left oblique view, where the left ventricle is enlarged posteriorly as well as downward, one can be more sure of left ventricular enlargement. In such a view, with right ventricular enlargement, the left ventricle becomes displaced upward. But in the present case, we cannot eliminate the possibility of left ventricular enlargement, especially in the presence of an apical systolic murmur which might indicate the presence of a ventricular septal defect which would give left ventricular enlargement.

The roentgen findings in the lungs are typical of pulmonary hypertensive vascular disease, with dilated proximal vessels and decreased vascularity of the peripheral lung fields.

I think, then, that this case is one of pure pulmonary hypertensive vascular disease, that the systolic apical murmur is a functional one, and that no significant interventricular septal defect is present. There will be found, at autopsy, right atrial and right ventricular hypertrophy, but no evidence of heart failure peripherally.

In general, among patients with congenitally malformed hearts, having large intracardiac shunts, in whom pulmonary hypertensive vascular disease is present, there are two distinct groups. In the first, the increase in pulmonary vascular resistance is present, presumably as an associated congenital anomaly from the time of birth. In this group, no good correlation is found between the size of the intracardiac shunt and the degree of pulmonary vascular obstruction. In a second group, that come to attention later in life, particularly in patients with a patent ductus arteriosus or an atrial septal defect, it appears that the many years of excessive flow through the pulmonary vessels hasten the ordinary aging processes and may give rise to pulmonary vascular obstruction.

This child may fall into the first of these groups, but, because of his syncope (an evidence of a rapidly advancing pulmonary vascular obstruction), I favor the idea that he will fall into a third group—that of idiopathic pulmonary hypertension with no associated cardiac lesion.

The proximate cause of death here is the critical decrease in pulmonary blood flow with a resultant right heart strain. The immediate cause of death may have been secondary to pulmonary vascular spasm, or a slight decrease in the pressure of the systemic venous return, which may have lowered the right ventricular filling pressure below a critical level. Since the high pulmonary pressure requires maximum

diastolic distention of the fibers, a high filling pressure would be required, and if this was lacking, the right ventricle could no longer develop sufficient intraluminal systolic pressure to overcome the vascular resistance. In either case, the final cause of death was a functional one.

DR. CRAIG.—Is there any way to tell, clinically, the difference between functional, and supposedly reversible, from structural, and presumably irreversible, changes in the pulmonary vessels—that is to say, spasm from anatomical change?

DR. GOODALE.—In this case, where the clinical signs are so unequivocally demonstrable, you will always find severe organic changes. In patients with a patent ductus, if there is no evidence of right ventricular hypertrophy by physical roentgenographic, or electrocardiographic examination, you can be certain that no organic pulmonary vascular change is present. Cases of atrial septal defect are most difficult to evaluate, because here right ventricular hypertrophy develops before any pulmonary hypertension. But here two signs are helpful. The first is the electrocardiographic evidence of right ventricular strain and the second is a palpable pulmonic second sound.

DR. ABRAHAM RUDOLPH.—I would agree that it appears unlikely that an associated ventricular defect was present in this patient. If a ventricular septal defect were present, blood would flow through the septal defect into the left ventricle and thus supply an adequate flow to the systemic circuit, decreasing the chance of syncopal attacks. The fact that this child, even in the critical stages of his illness, failed to show any significant cyanosis rules out any right-to-left shunt at the atrial level.

Although we have postulated a block in the pulmonary circuit, we have not placed this obstruction in anatomical terms, and it may be at the pulmonary arteriolar level, in the left atrium, or in the mitral valve, though the roentgen pictures would tend to rule out the latter. The changes in the arterioles could be due to embolization of tumor or other particles.

DR. GOODALE.—The principle that the presence of a ventricular septal defect acts as a safety valve in syncope is a sound one, yet in patients with atrial septal defects with pulmonary vascular disease, syncope is a common complaint. The appearance of primary pulmonary vascular disease following pregnancy has been related to thromboembolic disease in the pelvic vessels.

DR. RUDOLPH.—It should be remembered that patients with pulmonary hypertension are extremely fragile, and sudden demise may occur after relatively minor diagnostic procedures, such as cardiac catheterization, angiochoriography, venous pressure determinations, or, as in this case, bone marrow aspiration.

DR. CRAIG.—Is there any way of reversing the spasm in the pulmonary vessels of such patients?

DR. RUDOLPH.—The pulmonary vessels are unresponsive to most drugs. We have tried several preparations but have found no effective ones.

DR. CRAIG.—The child, at autopsy, had a heart which was three times the

normal size, with dilatation and hypertrophy of the right ventricle. The ventricular wall was 1 cm. in thickness, against a value of 0.5 cm. for the left ventricle. The major pulmonary vessels were greatly dilated and could easily be traced out to their secondary and tertiary branches in the periphery of the lung. There were gross atheromata in the main pulmonary artery. The muscular elastic arteries were most affected (Fig. 1) by intimal proliferation, fibrosis, hyalinization and marked narrowing of the lumen. Thrombi may be found in these narrow areas and, distal to them, a dilatation of the vessels or its branches may occur. Further thrombosis, endothelization and organization of such thrombi may also be present. These vascular changes may have some of the appearances of a glomus. The bone marrow contained an increased number of mature erythroid cells, consistent with an iron-deficiency anemia. There were an adequate number of megakaryocytes in the bone marrow. The decrease in circulating platelets may be due to an increased consumption of these elements in the lung in the numerous thromboses that were present. As Dr. Goodale predicted, no anatomical cause of the immediate and sudden demise was demonstrable and we agreed that the cause of death might have been a functional one.

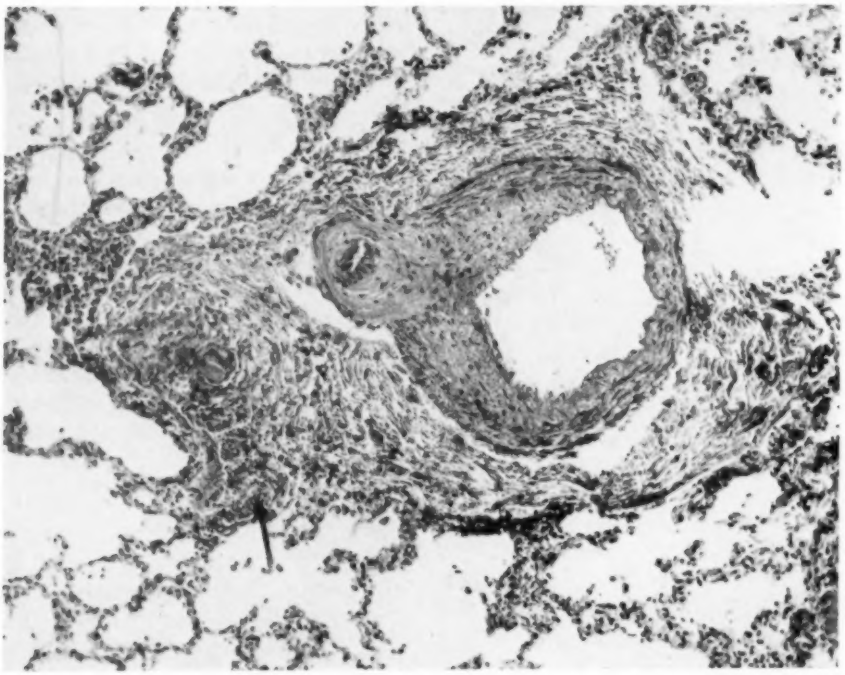

Fig. 1.—Lung. A muscular artery narrowed by an endarterial fibrous proliferation. A small occluded and recanalized artery adjoins a dilated but thrombosed, organized and partially recanalized thin-walled aneurysmal vessel (at arrow). (Hematoxylin and eosin. ×125.)

O'Neal and Thomas[2] have emphasized the importance of embolization and thrombus formation in cases of pulmonary hypertension associated with other cardiac lesions.

Owen's[3] series of cases of idiopathic pulmonary hypertension had, in nearly all instances, evidence of embolization or systemic venous thrombosis as a source for such embolization.

In this case, we have no source of embolization, but the picture is entirely consistent with repeated embolization of the lung.

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Special Article

MEDICINE AT AN AMERICAN INDIAN RESERVATION

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THE Fort Hall Reservation is in the southeast corner of Idaho. Here, only eighty miles from the atomic reactors in the Arco Desert, scientific medicine vies with magic and shamanism. The Shoshone and Bannock Indians of this reservation are of Uto-Aztecan stock, as are the Hopi, Paiute, Ute, and others, and were one people with the Comanches from whom they parted early in the eighteenth century. The Shoshones and Bannocks are believed to have migrated north from Mexico before the conquest, but it is difficult today to believe that at one time their culture was equal to that of any contemporary European culture. The cayuse has gone to make way for the jalopy, lipstick is used abundantly, and the Indians can vote and buy whiskey; but many still reject the white man's medicine.

In the early days there must have been some contact with the Spanish, as evidenced by the horse and trappings and even Spanish words in the Shoshone vocabulary. The first recorded history of contact with white man and his medicine starts with Lewis and Clark in 1805. The members of this expedition were trusted as no white man has been since that time, with good reason, and *The Journals* record many interesting observations. The medicine of Lewis and Clark was very little better than that of the Indians, and, as a matter of fact, was somewhat like it. Sweating and purging were their treatments in stock. Sacajawea, their Shoshone guide, became very ill and just managed to recover.

A few years later the Oregon Trail was established through this area, and along the trail came the white man with his diseases. There is an account by Edwin Denig, one of the early fur traders, telling of the introduction of smallpox among the Crows by a wagon train in 1833. The epidemic then spread to their neighbors, the Bannocks and Shoshones, and other Indian tribes. There are still stories of this epidemic; it is said that so many died that bodies were left to lie in the tepees without burial, and for many years ghost villages of tepees stood until they were destroyed by the elements and the bones were scattered.

When Washakie, the best known of the Shoshone chiefs, in 1868 signed the treaty of Fort Bridger which established this reservation, a provision was made that a doctor would be supplied. The first of these introduced smallpox vaccination just preceding an epidemic. The vaccination was so successful that even to this day immunizations against any disease are readily

accepted and "shots" are requested for nearly every illness.

PRESENT-DAY MEDICAL CARE

A hospital was built in 1923 and closed during the Second World War for want of personnel. No other physicians were assigned to the reservation. Room by room the hospital space was taken over by offices in which various governmental agencies carried out their work of making reports and filing multiple copies of reports. The old equipment and drugs, chiefly castor oil and calomel, were buried in a trench. Only two years ago an office was again opened for public health and medical care, in the remodeled basement of the former hospital.

With the closing of the hospital, physicians in the neighboring cities were asked to make bids to supply medical care. The superintendent was instructed to choose one of these, not necessarily the lowest bidder. This system of supplying medical care had been condemned in a Brookings report twenty years before, and it was as poor as might be expected. Occasionally the doctor taking the contract was capable enough, but dropped the contract when his practice became adequate. At times, the contract was taken by the local medical failures. In 1955, the last of the contract physicians resigned when the United States Public Health Service took over the medical care of the Indians.

Now the Indians of this reservation are allowed to choose any doctor they wish, or any hospital when necessary. They are supposed to pay for this medical care if it is at all possible; but not being conditioned to pay for medical care, they rarely do so. When the agency authorities are straining at the budget and screening requests for medical care carefully, a doctor who is too popular with the Indians may do more work than he can afford to do without pay. A few Indians have medical care insurance. Most often the agency arranges to pay for drugs and medical care. This is necessary since the average family income is only six hundred dollars a year, often obtained only from land rentals. Of the five hundred families living here, one hundred and twenty-five are carried on outright relief. Every effort is made to take advantage of other agencies that might help in medical care, such as the Polio Foundation, crippled children's services, and county funds. These agencies frequently make every effort to avoid helping with medical care, and may invoke petty and preposterous rules to support their stand, fearing that if they are too liberal they will be left without funds.

The population of the reservation is not so homogeneous as appears superficially, there being various groups of Shoshones in addition to the Bannocks. In the Bannock Creek area live the descendants of "Pocatello's band," renegades in Washakie's days. The last to be brought to the reservation were the Lemhi Shoshone. These groups are antagonistic to each other, distrustful and suspicious, so that it is difficult to get cooperation in many things, and especially in improving the local health conditions.

MEDICINE MAN AND WHITE DOCTOR

There are at least five practicing Indian "medicine men" on the reservation, but there are complaints that they no longer have as much power as their predecessors. For many diseases they are considered better than the

white doctor, particularly for those diseases like tuberculosis that require long periods of treatment. The medicine man gives the patient a treatment one day and he is supposed to be better the next day. If he is not better, it is because he has not believed enough in the treatment. I suppose that if I considered myself a member of a subject race and required medical care, I too would first seek help from one of my own people.

The medicine men enjoy some reputation as specialists in certain fields, there being one considered better for diseases of the feet, another for headaches, and so on. It is sometimes difficult to see why the medicine men are so popular, for while ceremonies and prayer might be good for imaginary or psychosomatic illnesses, the Indians are not prone to develop these complaints. In truth, they tend to disregard the most serious illnesses and physical difficulties until they are nearly moribund, and can suffer the most terrible injuries without a murmur of pain.

When the white doctor is seen, the consultation apparently takes on many of the characteristics of a visit to the medicine man. In warfare the Indians always attacked at dawn, but the visit to the doctor may take place at any hour of the day or night. The concept of time is not well developed, and appointments are rarely made and even more rarely kept. Getting transportation is difficult, and driving to the town requires a car that has not only gasoline but also brakes. For the Indian, the transaction takes place in a foreign language in which he may know little more than enough to buy a loaf of bread or a jug of wine. Indian medicine men know everything, and ask no questions, so only a minimum is told the white doctor. The chief complaint consists of a pain in some part of the body, or perhaps a rash or fever. Disease entities, even those as common as mumps or measles, are not often recognized. The duration of the illness is either "long time" or "short time." Previous treatment is neither discussed nor admitted. Children are stripped for examination without question. The treatment is given. No questions are asked regarding the medicine or the diagnosis. The patient leaves. This sort of visit may be therapeutic for the doctor himself, who is often set upon by some anxious white mothers to give a medical education and a psychiatric séance with each visit. The doctor who cares for Indian patients must accept the patient without criticism of the treatment that has preceded the visit and must be prepared to have his offers of care refused if they do not appeal to the patient.

Bleeding is done even for minor illnesses. It would seem unlikely that this was introduced by the white man, for bleeding was no longer in fashion in the period following Lewis and Clark's visit. There are certain Indians who are especially adept at bleeding. A special small knife is used, and a string is tied about the blade so that it will not penetrate too deeply, in the manner of a "guarded scalpel." The knife is then boiled, perhaps in an attempt at sterility, or as part of a ceremony. In children, where veins are difficult to approach, a small stab wound is made above the hairline, which bleeds profusely. In adults the antecubital veins are pierced. This bleeding undoubtedly contributes to the demise of the patient. On occasions Indians will ask white doctors

to bleed them, a request which is always refused.

Herbs are used, the most frequent being the common sage, which is certainly available. Willow leaf poultices are used for skin diseases, particularly impetigo. The poultice may have some analgesic qualities because of the salicylic acid content. There is a tendency to use the white man's patent medicines more than the older Indian herbs. Ointments and lotions are preferred preparations. Powdered, colored minerals are applied to diseased parts. Older people are partial to skunk fat. Acupuncture is practiced with multiple incisions made over the painful part or the supposed seat of the illness, so that children with fever may have multiple wounds of the forehead.

TRIBAL CEREMONIES

Ceremonies are held to protect the individual and the community. The sun dance is the most important and most widely publicized of these ceremonies. The Shoshone sun dance is a delicate version of the Sioux rituals as carried out by Sitting Bull when he made big medicine on the banks of the Rosebud. Then the warriors danced about a pole on tethers passed through their pectoralis muscles, gazing at the sun until finally exhausted, when they had visions. The Shoshone dance has survived because of its mildness, and is held almost entirely as preventive medicine and to effect cures. The efficacy of the dance is said to be greater when the dancers are of high repute, and efforts are made to have members of the tribal council dance. There is a widespread belief among the Indians, even those "who wear shoes instead of moccasins," that the masochistic ordeal of four days of dancing and fasting without even water will do good for the dancers and for those for whom they intercede. "It is better than a doctor's prescription for tuberculosis and rheumatism." In the past, each dance was followed by an outbreak of diarrhea among those who came to view the dances and eat and drink in the nearby booths.

During the dances, patients are brought for treatment by the sun dance leader. Like other medicine men, the leader has no particular training or background, but he has had a dream or vision instructing him to head the dances. The tribal council picks the leader who has related the most convincing dream or vision.

In mid-winter when it is usually 20 degrees below zero, a "warm dance" is held to make warm weather return with improved health. The dancers are led in a circle dance by the medicine man, but the dancers appear to be more interested in the social opportunities of the dance than in the ceremonial aspects.

PEYOTISM

Peyote is commonly used for the most serious illnesses, particularly tuberculosis. Sometimes the patient will take peyote and isoniazid and PAS. The peyote cult is under the control of the Native American Church, a well-organized group incorporated in the state of Oklahoma. The church introduced its services into Fort Hall in 1930 and sends officials of the church there periodically. The Native American Church has considerable good ethical influence, and the members of the cult are the Puritans of Fort Hall. Peyotism as a religion is said to have been present in Mexico before the Spanish conquest. Within forty years after the arrival of the

Spaniards, the ceremony had taken on many of the characteristics of the Mass and the priests made an attempt to stamp out the practice.

Peyote is taken during a ritual. The sick patient and his friends gather in a tepee erected for the ceremony. A fire is started in a crescent-shaped fireplace, the fire is sprinkled with evergreen boughs, and the peyote is blessed and passed about from person to person. It is taken in the same way that bread and wine are taken during the Mass, for it is said that God put some of His Holy Spirit into the peyote. It is also believed that peyote without the ceremony will not be efficacious, and if the patient does not believe, harm will be done. The church is active among the Apaches, Omahas, Kiowas, and other Shoshone groups. A very similar ceremony has been described using the mescal bean.

Peyote is obtained from a cactus native to the Rio Grande Valley. The top of the cactus is cut off and dried so that it looks like a button. At one time it was feared that the cactus might become extinct, but it is evident that this is not likely to happen since it has survived several centuries of harvesting. Attempts have been made to cultivate the plant, but this is not necessary. The cactus is sometimes raised in tin cans at Fort Hall and kept as house plants.

The pharmacologically active substance of peyote is mescaline, an alkaloid that causes hallucinations, anxiety, tremors, and other neurological signs. It does not cause addiction and there are no withdrawal signs. After a patient has been given peyote, it is often several days before the true character of an illness becomes evident. Mescaline is very closely related chemically to lysergic acid diethylamide. The possession and shipping of peyote are illegal, although it is continually being shipped by parcel post. The single attempt of the Federal Government to enforce the law in the courts failed because of the religious character of the ceremonies.

FAMILY AND CHILD RELATIONSHIP

At one time a Shoshone woman was allowed to choose a male protector when her husband was absent on hunting or war parties. Marriage is still a loose alliance and illegitimacy is not censured. If the current mate does not want the children of some previous match or even his own child, he makes this fact clear and the children are given to some relative or abandoned. Grandmothers or aunts are favorite choices, and nearly as many children are brought up by near relatives as by their own mothers, a surprising state of affairs in any human or other mammalian group. All the maternal aunts are also called *biah*, or mother, so that a child will say "I have four mothers" or "I have three mothers." The mother herself is just another aunt. It would appear that the children should all suffer from maternal deprivation, but this is not so. The children are docile, trusting, and tolerant. They are extremely kind to each other. They accept hospitalization without protest, and, apparently from having been exposed to so many adults, they will accept any other adult as a mother substitute. In the pediatric ward they follow the nurses or any white child's mother who pays any attention to them. Indian mothers visit their children infrequently. Later, the adults show the traits the psychiatrists would predict. The typical Shoshone adult lacks

warmth in his associations with others, is poor at abstract thinking, and is of a suspicious, hostile nature.

It often appears as if maternal feelings are just strong enough to preserve the race. The death of an adult is accompanied by a great display of grief, which is probably ceremonial since the old and feeble are often left out in the sagebrush to die without help. The death of a child evokes very little outward reaction. It might be expected in a civilization that looks only backward that children, who represent the future, do not seem important. Long years of high infant mortality may make them feel that children are expendable. The birth rate is forty per thousand, or twice the rate for the surrounding white population; but the crude death rate has also been nearly twice that of the general population. Nearly every mother's record shows the death of three or four infants. Occasionally a mother will openly admit she does not want her child and make every effort to abandon it. When a girl is wanted rather than a boy, the child will be kept in long hair and ribbons until the mother can no longer pretend he is a girl. Children are sometimes adopted out into white families without a sign of guilt. Infanticide or, at least, severe neglect is practiced, so that children with a congenital defect may be seen only once and then never again. Twins are unwanted and considered bad luck, and they certainly were when a mother with twins couldn't run fast. The second born is a "dog" to be sent out to anyone who will have him. A child born soon after another child is also very likely to be given away.

Parents are permissive to an extreme degree so that there is practically no discipline. Clark stated that this was done "lest they break the spirit of the child." Today they say it is so that the children will grow up to like their parents. Much of the discipline, such as it is, is left to the maternal aunts and grandmother. The white man's school is the first real discipline, and the Indian child promptly withdraws into an almost autistic state where he sits quietly surrounded by his white peers speaking a foreign language. Later, when he is picked up for joy riding and sent to the local reformatory, which is almost an all-Indian school, he may get his most valuable education in some trade. Ridicule is the strongest restraining influence, severe enough to drive a teen-ager, or even an adult, to suicide. On the other hand, a child who receives an injury is not picked up and petted, so that Indian children are not conditioned to crying as are most white children. If he cries at all, an Indian child cries without conviction. Indian children never suck their thumbs. They never carry around an old blanket or particular toy. They do not have toys.

Surprisingly enough, almost all children are born at the hospital, with only a few being born precipitously at home. Births and deaths are well reported; the benefits of being on the tribal roll are enough to make birth reportable, and the death benefit of one hundred twenty-five dollars is enough to make death promptly reportable.

THE "MOON HOUSE"

When a mother returns from the hospital with her child, if she follows the old customs she must spend some time in the menstrual hut or "moon house." Blankets and food are deposited in this hut before the mother

leaves for the hospital, and with these accommodations she must be satisfied when she returns. This is an incentive for the mothers wishing to go to the hospital and staying there as long as possible, thus shortening the stay in the moon house. In cold weather the mother and child frequently return to the hospital with pneumonia. Until recently some women insisted on delivering their children in a squatting position. This was encouraged by one of the local doctors who felt that the squatting position was more physiologic, and constructed a special table to allow the mother more comfort in this position. It has been shown that gravity is an aid in this position and it may be true that there are fewer birth injuries. At the present time most mothers accept the usual delivery room techniques.

Young girls, too, must stay in the moon house during their menstrual period. This practice is often responsible for their staying away from school, for they are reluctant to parade out of the hut to the school bus each morning. Poor clothing, language difficulties, and no recognition for school achievements also make for poor school attendance and many school failures.

Fathers generally do not visit mothers during their hospital stay, this being a carry-over from the moon house taboo. The umbilical cord which falls from the child is saved and buried at the foot of a tree. The growth and fate of the tree are then considered to mirror the well-being of the particular person. Occasionally the mother will try to remove the cord while the child is in the hospital and brought out for feedings. At one time the placenta was buried, too, but this practice has been given up since the placenta is not obtainable from the hospital.

INFANT CARE

Most children are breast fed. Any child placed on a formula is very likely to be admitted to the hospital with diarrhea. Water is usually not boiled because "Indian babies are strong. White babies are weak and need their water boiled." Seventy-five per cent of the water available is unsatisfactory for drinking. Often water is taken directly from the irrigation canals. Diarrhea is difficult to treat in these children. They have a thick layer of subcutaneous fat which makes clinical judgment of the state of hydration difficult and children often die from diarrhea without appearing ill. I do not know if this thick, fatty layer is due to diet or a racial characteristic. A fair number of cases of diarrhea are due to paratyphoid or even occasionally to typhoid. Getting a stool specimen when looking for carriers is nearly hopeless since "a real Indian won't give it to you; it belongs to him."

The child is carried about in a cradle board as soon as the mother is up and around. The infant accepts the transfer from the narrow confines of the womb to the restraints of the cradle board without protest. Later, when the board is used mainly to take the child out from the home, he is as pleased to be laced into the board as a city-bred dog is to be taken out on a leash for his walk. Rickets is rare so that it is unlikely that the board was used to prevent deformities as was swaddling in European cultures. In the old days it was said that a child

carried in a cradle board was toilet-trained early and vigorously to prevent soiling of the mother. Now the children are wrapped in a final layer of plastic sheeting before being laced into the cradle board, and toilet training is a very, very late affair.

Malnutrition is unusual, even in the most unkempt and neglected children. "A skinny Indian has tuberculosis" is a local medical cliché and is fairly accurate. In the old days buffalo and salmon were available for food, but even then most of the early records report the near starvation of the Indians during certain seasons at least. A great portion of the food was at that time obtained from berries and roots, particularly the camas lily. It was because of this that these Indians were called "diggers." At the present time there is no closed hunting or fishing season and until recently even the 6-month-old children were fed fish, duck, or venison. There has been a recent shift to canned baby food following dietary instructions by health nurses and schoolteachers. During the winter months, jack rabbits are killed and tied to a pole where they freeze, to be picked like grapes from the cluster as they are wanted. Fresh cow's milk is rare, but sometimes evaporated milk is bought for the children. Mothers often ask that their children not be given milk while in the hospital because they will not get any at home when they return. Powdered milk is being introduced. Small game has been a part of their diet, but with the recent increase in land cultivation game is becoming scarce. There are few food taboos, except "us Indians don't eat pheasants." At one time eating of meat during the menstrual period and post partum was thought to bring on a fatal hemorrhage, but this is no longer believed. Vitamins are given to the children by the health nurses and are eagerly accepted. Vitamin deficiencies are extremely rare. All in all, what dietary instruction they have had has only served to make their nutrition worse, and it would have been better to have left them to their own devices.

SOME HEALTH PROBLEMS

Tuberculosis is the most serious health problem. Five hundred contacts are known or one out of every four. There is nothing in the Indian tradition regarding tuberculosis, and it is almost certain that tuberculosis did not exist here before the coming of the white man. The discoveries of Koch and Pasteur are unknown on the reservation where one "just gets tuberculosis." The treatment with the white man's medicine is long and difficult and even painful when streptomycin is given, so that treatment is often refused. Hospitalization generally requires going to the State Hospital at Gooding, Idaho, or the Indian Service Hospital at Tacoma, Washington. There is a great fear of traveling distances, which perhaps dates back to the days when travel meant an encounter with the hostile and usually stronger Blackfoot or Crow. Therefore, hospitalization is often refused, even when beds are available. Occasionally, outpatient treatment will be accepted, but it is just as often refused, since it is believed that the drugs will interfere with peyote. Several years ago BCG vaccine was administered to some children, but the official stand is against its use.

Venereal disease is common, but treatment is very readily accepted and

congenital syphilis rare. Clark questioned the Shoshones regarding venereal infections and felt they existed, but was not able to decide which infections were present. Penicillin not only is accepted for venereal infections but is usually requested for nearly any illness. On occasion x-rays are requested with the belief that they have some therapeutic values. Sometimes they are used only to direct the shaman's treatment. Many of the older people wander about nearly blind from trachoma scars. Few cases are found now, so that it appears as if the disease is finally disappearing, or it may be that we do not recognize early cases which are mild at the start in this cool climate. Diabetes is common in adults, usually mild, and probably due in some measure to the frequent obesity, but no cases are known among the children.

At the present time every effort is being made to assimilate the Indian as rapidly as possible, with the idea that when he is assimilated he will no longer be a problem. It is felt that his efforts to obtain medical care may be used to further his assimilation. The quality or availability of the medical care is sometimes only secondary to the advance of assimilation and termination of the Federal services. Established customs are destroyed and inferior methods are used. Customs which are harmful are not suppressed, as the use of the menstrual hut. The Native American Church and peyotism are protected under the guise of freedom of religion.

Education might start with hygiene instruction on a third-grade level. Funds for medical care are wasted without economic improvement and without better toilet facilities and water supplies. Personnel dealing with Indian health problems often have great technical skill but no understanding of the Indian's resistance and racial background. There are others who have great humanitarian motives but no technical information or ability, and these people often cause the greatest harm.

I am indebted to Mary Lou Skinner, health educator, Bureau of Indian Affairs, and to Dr. Sven Liljeblad, anthropologist, for much of the information reported in this paper.

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Comments on Current Literature

ADENOVIRUS PNEUMONIA

THE adenoviruses were first recognized as the causative agent in latent infections in human tonsils and adenoids, the original members of this group, called AD viruses, having been recovered from normal adenoidal and tonsillar tissue undergoing spontaneous degeneration in tissue culture. Shortly thereafter, closely related strains of virus were isolated in cases of acute undifferentiated respiratory disease (ARD) among military recruits, and from patients whose chief complaint was catarrhal inflammation of the mucous membranes of the eye associated with fever and pharyngitis. The designation, APC viruses (adenoidal-pharyngeal-conjunctival), was suggested for the entire group. Recently this designation has been changed by common consent to adenoviruses. To date the group comprises about eighteen distinct antigenic types which share a common complement-fixing antigen, and the members of the group are being assigned to numbered serologic types based on virus neutralization tests. In addition to the strains isolated from adenoids and tonsils grown in tissue culture, adenoviruses have been recovered from throat secretions, conjunctival exudate, mesenteric lymph nodes, and stool specimens.

The occurrence of these viruses in the adenoids and tonsils of children of preschool and early school age is common; one or more types of virus have been isolated from well over half of the specimens tested in this respect. These agents seem to be present in "normal" tissue in a latent or inactive form; their presence can be detected only when fragments of adenoidal and tonsillar tissue are cultivated in vitro. After a period of time, the outgrowth of the original human cells degenerates, and the viruses can be subcultured in HeLa or other cell strains. Adenovirus types 1, 2, and 5 are recovered most frequently from these normal tissues. Pharyngoconjunctival fever seems to be associated with type 3 adenovirus, but the illness may result also from infection with types 4 and 7. Epidemic keratoconjunctivitis (EKC, the so-called shipyard eye, sometimes epidemic in industrial plants and shipyards) has been associated apparently with several types: 2, 3, 6, 7, 8, 9, and 10. Recently, evidence has accumulated which seems to incriminate particularly type 8 adenovirus in this disease. Adenoviruses also may be the cause of at least one form of primary atypical pneumonia.

Among military personnel, adults and young recruits in the armed forces, outbreaks of disease caused by the adenoviruses have been relatively common: in the United States, in Britain, and in Europe. Among the civilian population, however, children appear to bear the brunt of the attack in the more serious adenovirus infections. A recent report from Paris, France, is interesting and timely: "Severe and Fatal Pneumonia in Infants and Young Children Associated With Adenovirus Infections" by Chany, Lépine, Lelong, Le-Tan-Vinh, Satgé, and Virat.[1] This informative article in the *American Journal of Hygiene* for May, 1958, deals with an outbreak of pneumonia associated with adenovirus type 7a, which occurred during the winter months in an overcrowded charity ward of the Hôpital

St. Vincent de Paul in Paris. Investigative studies were possible through the cooperation of the Virology Section of the Pasteur Institute and the Pediatric Service of the hospital. Virus typing was confirmed by one of these authors during tenure as a Rockefeller Foundation fellow in the United States at the laboratories of Drs. Huebner and Rowe, National Institutes of Health, Bethesda, Maryland.

The Hôpital St. Vincent de Paul consists of three groups of buildings, one group of which serves as a temporary residence and center for the medical care of orphans and abandoned children in the Paris area. This division cares for children committed to Public Assistance prior to their placement in foster homes. The children occupy open wards, grouped according to age; most of them stay no longer than 2 to 3 weeks. Orphans and abandoned children showing any signs or symptoms of acute illness are admitted to a special hospital ward. Ill patients admitted from the general population are cared for in an entirely separate building. There is no overlapping or exchange of hospital personnel, including doctors and nurses. In late December, 1955, an increased incidence of pneumonia was noted in a particularly overcrowded Public Assistance ward. During the four months immediately following, more than 20 cases of pneumonia occurred in approximately 125 children passing through this ward. Some of the cases early in the outbreak were not brought to the attention of the authors. Adenovirus type 7a was identified as the infectious agent either by direct isolation or by demonstration during clinical course of increasing titer of antibody to adeno-type 7a, or both. Serum specimens on all patients were tested against strains of adeno-type 7a being isolated during the epidemic, as well as against a standard strain. In four of the cases the clinical illness was very severe from the onset, and in three of these, the outcome was fatal. This type of adenovirus infection appeared to be more severe and more prevalent in patients of the age range, 6 months to 4 years; pneumonia due to adenovirus was observed only once in a child under 6 months of age, and no case was observed in children over the age of 5 years.

This epidemic of adenovirus pneumonia was confined to the open wards among orphanage children of the Public Assistance section of the hospital, and did not spread to other sections, nor to other areas of the hospital center. More than one year later, eight sporadic cases were encountered in the open wards of this same Public Assistance division, between June, 1956, and January, 1957. In four of these eight patients the diagnosis was made by complement-fixation tests, and in four of the cases the virus was recovered from the patient's throat. In these sporadic cases of adenovirus infection two types were incriminated, type 4 and type 2. Likewise during the month of June, 1956, a family outbreak of adenovirus infection (type 7a) occurred which involved three children, aged 4½ years, 21 months, and 3½ months, the eldest of whom died. The present authors collaborated with others[2] in the investigative studies of these cases. The young infant, 3½ months of age, experienced a mild upper respiratory infection and pneumonitis, with complete recovery; the child of 21 months had a serous pleural effusion similar to that observed in the cases encountered by the authors during the epidemic; the 4½ year-old child who died suffered from severe viral pneumonia and showed in addition clinical signs of encephalitis.

The clinical manifestations observed in all these cases of adenovirus pneumonia were similar: acute onset with pharyngitis and cough, and temperature rise to 38° C., 39° C., or above. The temperature curve was characteristically oscillatory in form and was not affected by antibiotics; the physical and radiologic pulmonary findings observed were those associated with a severe pneumonitis, persisting after

the general clinical symptoms had subsided. In some instances, conjunctivitis was a feature of the disease, and occasionally a morbilliform eruption without secondary desquamation was observed. The findings at autopsy in the fatal cases are described as specific pathologic features: a characteristic bronchial necrosis and an intranuclear inclusion-body pneumonitis very similar to that reported in infants by Goodpasture and his associates[3] in 1939. The pathologic findings in one particular case are discussed by the authors in some detail. Type 7a adenovirus was isolated from a spinal fluid specimen obtained on the day before death and was recovered from brain and lung tissue taken at autopsy. Bronchial necrosis was marked with "striking cytologic changes in epithelial cells of the bronchi, submucous glands, and alveolar walls." In the brain, perivascular inflammatory lesions were widespread, with some meningeal infiltration by mononuclear cells; the cytologic changes in brain tissue were considered nonspecific. Laboratory procedures carried out for purposes of differential diagnosis included complement-fixation tests for ornithosis, psittacosis, and Q-fever; hemagglutination-inhibition tests for influenza viruses, A, A′, B, and C; and tests for cold agglutinins and antistreptolysin titer. Strains of adenovirus isolated could be propagated successfully in tissue culture with the production of "rosette-like" cells and the occurrence of intranuclear inclusion bodies similar to those observed in lung tissues taken at autopsy.

In a critical discussion of the observations made during these outbreaks of adenovirus pneumonia, Chany and his associates[1] call attention to the rapid progression which may characterize this type of infection in the pediatric subject, stressing the consideration of adenovirus vaccine for use in the susceptible age group: "In view of the severe manifestations in the cases associated with adenovirus, the question arises as to whether or not a special population, such as the one in which most of our cases occurred, should be protected by an adenovirus vaccine."

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Erratum

In the article by James N. Etteldorf, M.D., Constantin Missirliu, M.D., and Walter Fleischmann, M.D., entitled "Adrenogenital Syndrome Due to Congenital Virilizing Adrenal Hyperplasia," which appeared in the October issue of the JOURNAL, on page 400, column two, the paragraph beginning on line 5 should read as follows:

"Some evidence points to the fact that impaired hydroxylation of C_{11} interferes with the synthesis of hydrocortisone, and an increased production of desoxycorticosterone is believed to account for the cases in which there is hypertension (five out of sixty-five in the Wilkins series).[18, 19]"

HENRY FREDERIC HELMHOLZ
(1882-1958)

WITH the death of Henry Helmholz on August 19, 1958, pediatries lost one of its best-known and respected leaders. He was born in Chicago, August 24, 1882, and his death from cardiac disease was within a few days of his 76th birthday. After graduation from the University of Wisconsin in 1902 with the B.S. degree, he studied medicine at Johns Hopkins, receiving his M.D. degree in 1906. After a year's Fellowship at Hopkins he spent two years abroad at pediatric clinics in Berlin, Breslau, and Vienna. In 1910 he started pediatric practice in Chicago, where he became Assistant Professor of Pediatrics at Rush Medical College and Medical Director of the Children's Memorial Hospital. He was intensely interested in child health and for ten years served as Director of the Chicago Infant Welfare Society, and was also on the Executive Board of the American Child Health Society. In 1921 he left Chicago to become Head of the Pediatric Section of the Mayo Clinic at Rochester, Minnesota, where he made his home until his death, retiring "on age" from his clinic position in 1947. Throughout his many years of clinical work in Chicago and Rochester he maintained a great interest in pediatric research and contributed many studies, particularly in the field of kidney and bladder infections. After his retirement from clinical work he spent 1948 in Europe as chief consultant to the U. N. Children's Emergency Fund, and 1952 to 1955 was chairman of the committee on public health of the P.T.A., taking an active part in the campaign for the fluoridation of water.

Dr. Helmholz was a member of many medical societies in this country and abroad. He was elected to membership in the American Pediatric Society in 1914 and was president in 1937. As a Founder Member of the American Academy of Pediatries he wrote the original constitution, and served as president of the Academy 1938-1939. He was one of the original members of the American Board of Pediatries. Among other of his societies were the Phi Beta Kappa, Sigma Xi, and Alpha Omega Alpha honorary fraternities. From 1917 to 1924 he was Editor of the *American Journal of Diseases of Children* and continued on the Editorial Board from 1926. His "bibliography" lists many scores of published papers, and he contributed sections to Abt's and to Brennemann's Systems. The international aspects of pediatries were another of his many interests, and he was president of the 5th International Congress of Pediatries held in New York in 1947.

Such is a sketchy outline of the active and useful medical life of Henry Helmholz. To those who were associated with him during those years, the thing that stands out and will be remembered most was the man himself, his fineness of character, his love for children, and the idealism that motivated his work and interests. He was respected by all and loved by those who were privileged to close friendship.

He is survived by his widow, Isabel Lindsay Helmholz, to whom he was married in 1907, and three sons and a married daughter. Two of his sons hold professorships in American universities.

Correspondence

To the Editor:

I enjoyed the recent paper entitled "Marchesani Syndrome" by Drs. Zabriskie and Reisman in your JOURNAL (**52**: 158, February, 1958).

I am aware of three further reported examples of this interesting syndrome not included in their compilation. Weill described (Ann. d'Oeul. **169**: 21, January, 1932) a dwarfed 42-year-old woman with ectopic lenses and very small hands. McKusick on page 72 of *Heritable Disorders of Connective Tissue* (St. Louis, 1956, The C. V. Mosby Co.) illustrated a father and daughter whom he felt displayed the features of this syndrome.

My interest in this syndrome stems from a study of a family in which both Marfan's syndrome and the Weill-Marchesani syndrome coexist. This study, as yet incomplete and unpublished, concerns 7 generations of a Canadian family. To date, I have found 31 members of this family who have demonstrated the signs of Marfan's syndrome and 2 members who have displayed the signs of the Weill-Marchesani syndrome. In a family in which Marfan's syndrome is rampant, it seems an unlikely coincidence that two examples of the Weill-Marchesani syndrome should arise as new mutants. This observation leads me to suggest that the morphologic differences between these two syndromes are of insufficient importance to justify any genetic difference between them.

Since the coexistence of these syndromes in the same family has not been reported previously, the validity of this conclusion must await further confirmation.

DORRANCE BOWERS, M.D.
Kelowna, B. C.

News and Notes

Dr. Edward B. Shaw of San Francisco has been appointed professor of pediatrics and chairman of the department at the University of California School of Medicine, San Francisco. Dr. Shaw has been a member of the school's clinical staff since 1921 and is leaving private practice to devote full time to university service. Since 1928 he has been chairman of the department of communicable diseases at Children's Hospital in San Francisco.

The **University of Texas** M. D. Anderson Hospital and Tumor Institute and The University of Texas Postgraduate School of Medicine will hold a *Clinical Conference on Cancer Chemotherapy* Nov. 14 and 15, 1958. Among those taking part is Dr. Sidney Farber of Boston. For details write M. D. Anderson Hospital and Tumor Institute, Texas Medical Center, Houston 25, Texas.

The **Lead Industries Association** will hold a *Conference on Lead Hygiene* at the Drake Hotel, Chicago, Nov. 6 and 7, 1958. Attendance at the Conference will be limited to 150 persons. To assure admission, those who wish to attend should so signify, by postcard or otherwise, as promptly as possible. Reservation applications for rooms at the Drake Hotel will be sent only to those who have done so. The address of the Association is 60 East 42nd St., New York 17, N. Y.

The **International Children's Centre** (Chateau de Longchamp, Bois de Boulogne, Paris-XVI^e) announces the following awards:

The Guigoz Fellowship.—The 1958-1959 fellowship to promote nutritional research founded by the Guigoz Works was awarded to Dr. Jean Chagnon (Canada). The 1959-1960 fellowship will be awarded in the spring of 1959. The applicants are required to send to the International Children's Centre (a) *a curriculum vitae* setting forth their work on biological and social problems concerning

feeding or nutrition of infants and children, (b) *an introduction letter* from one of their Masters, (c) *a description of the studies* which they wish to pursue with the help of the Guigoz fellowship. The applicants should have a sufficient command of the French language.

The Nestlé Fellowship.—A research fellowship of one million francs is awarded every year by the French Nestlé Company to a physician who wishes to specialize in the field of nutrition.

For the year 1958-1959 the panel of judges awarded the fellowship to Dr. André Frederich (Lyons). The 1959-1960 fellowship will be awarded in the spring of 1959. The applicants are requested to send to the International Children's Centre (a) *a curriculum vitae* setting up forth their work on the biological and social problems connected with feeding or nutrition of infants and children, (b) *an introduction letter* from one of their Masters, (c) *a description of the studies* they wish to pursue with the help of the Nestlé fellowship. The applicants must have a sufficient command of the French language.

The Gallia Prize.—The Prize founded by the Gallia Works to reward a study on the problems of nutrition of the African child was awarded to Dr. R. Cabannes and Dr. J. Clausse of Algiers by a Panel of Judges who met at the International Children's Centre, with Professor R. Debré in the Chair. Drs. R. Cabannes and J. Clausse will carry out their work on nutrition of the African child under the guidance of Professor Sarrouy, Dean of the Algiers Faculty of Medicine.

The **New York City Department of Health** has established a "*Multiple Birth Roster.*" The Roster is intended to be a source of information for research workers in the fields of genetics, child development, etc. The Department will cooperate with researchers to supply them with some data which may be helpful to them to initiate genetic studies. All multiple births involving at least two live infants are included in the Roster. All the identifying, demographic, and pregnancy information available on the birth certificate of each infant is punched on a tabulating card. A photostatic copy of the complete record of birth is also in the register, so that details not available on the punched card may be conveniently abstracted. The Roster will be kept up-to-date in three respects: adoption of a child, deaths during the first year of life, and data fed back to the Roster by the individual researcher. The Roster was initiated as of Jan. 1, 1958, and will be continued indefinitely. At a later date an evaluation will be made to determine whether its usage by researchers warrants its continuation. Researchers requesting information from the Roster will be expected to adhere to such requirements as the Department may deem necessary. All requests will be reviewed as to the qualifications of the investigator and the value of the proposed study. Investigators may be asked to allocate clerical staff to assist in selecting the data requested. Facts elicited by home interviews and/or abstract of records are to be made available by the researcher to other researchers to avoid duplications of efforts. Formal requests should be submitted to Dr. Harold Jacobziner, Assistant Commissioner for Maternal and Child Health Services, New York City Department of Health, 125 Worth Street, New York 13, N. Y.

The **Betty Bacharach Home** in association with the pediatric, medical, and psychiatric departments of the **Jefferson Medical Center** has organized a unit for the treatment of intractable asthma in children. Children with perennial asthma of more than one year's duration and who are refractory to hyposensitization and other forms of medical treatment are eligible for admission.

The Betty Bacharach Home is ideally suited for this project. The asthmatic unit is a separate entity. Environmental control is excellent and all facilities, including schooling, are available within the institution. Absecon Island, on which the Home is located, is a relatively pollen-free area. Children from 5 to 15 years will be considered for admission. The Betty Bacharach Home will underwrite the cost for all children admitted to the unit. For further information contact Mr. Simon Lippman, Executive Secretary of the Betty Bacharach Home, Atlantic City, N. J.

Books

Tuberculosis in White and Negro Children. Volume I. Roentgenologic Aspects of The Harriet Lane Study. Janet B. Hardy, M.D., C.M., Cambridge, 1958, Harvard University Press, 119 pages. Price $7.50.

Data for both this volume and Volume II (The Epidemiological Aspects) are derived from experience gathered during the course of a study at The Harriet Lane Tuberculosis Clinic, established in 1928 by Dr. Edward A. Park at Johns Hopkins Hospital. The study is based on observations at the pediatric outpatient clinic on tuberculous children admitted for treatment between 1928 and 1944.

The introduction to Volume I deals with the organization of the study and interesting and comprehensive definitions of terminology used in this report.

The study utilized the records of 190 white and 401 Negro children admitted to the clinic during infancy because of demonstrable tuberculous infection and also those of their 738 older siblings who had not reached the age of 15 years when infection was discovered.

There is a carefully construed discussion of the anatomy of the lungs, with diagrams, methods of roentgenologic examinations and interpretations, giving, in a most comprehensive and interesting manner, the various factors influencing the reading and interpretation of the films.

This is followed by a series of roentgenograms of the chests of normal children with normal structures and artifacts for comparison with films on pathological findings. There are numerous, well-selected reproductions of various manifestations of tuberculosis in childhood with differential diagnosis, including concise and practical descriptions and interpretations of the films pictured.

Section II deals with bronchoscopy and bronchography, with indications for these procedures and conditions requiring their use in differential diagnosis. Procedures for both of these diagnostic aids are discussed most comprehensively, with diagrams and photographs.

Tuberculosis in White and Negro Children. Volume II. Epidemiological Aspects of The Harriet Lane Study. Miriam E. Brailey, M.D., Dr.P.H., Cambridge, 1958, Harvard University Press, 100 pages. Price $4.50

The Volume likewise is divided into two sections.

Section I consists of epidemiological studies based on The Harriet Lane Study, using the records of 437 white and 892 Negro children, admitted to the clinic between 1928 and 1944. The follow-up study was continued until 1950.

Methods of sampling, methods used in selection of infected children over a long period of time, and trends in the community studied are discussed prior to the elaboration of the organization of The Harriet Lane Study. Statistical data are given, utilizing the findings on these children on physical examination and x-ray studies, and correlations are given with relation to other factors, such as race, age at which infection was discovered, and extent of lesion. Families of both races lived in overcrowded homes and were usually unable to pay for medical care. The majority of children in this study were under outpatient supervision.

Morbidity was studied by analyzing chest x-ray findings at the time infection was discovered as to age, race, and extent of lesions (nodal, parenchymal, and extrapulmonary lesions).

Mortality over the 15-year period was studied as to risk by years, sex, and extent and type of lesion for both races, the mortality being nearly 9 per cent in white and 22 per cent in Negro children found to be infected before 3 years of age. The risk was concentrated in the first year of life for nearly 100 per cent of the whites and 70 per cent of the Negro children. Mortality over the 15-year period in general was 0.8 per cent for white and 8 per cent for Negro children. Of children over 3 years of age when infection was discovered, 39 per cent were due to extrapulmonary tuberculosis, 5 per cent to postprimary tuberculous pneumonia, the latter being the subject of Section II of this volume.

Section II. "The Risk of Developing Reinfection Pulmonary Tuberculosis in the Experience of The Harriet Lane Tuberculosis Clinic."

The majority of children in this study had come to the clinic because of known household exposure to tuberculosis. About 60 per cent were less than 5 years of age on admission, and 43 to 45 per cent were under 3 years of age. Most of the infections under 3 years were recent, but duration could not be determined for those between 3 and 15 years.

X-ray examination was the basis for determining reinfection tuberculosis, although home visits and family follow-ups were made. Tables and graphs show probabilities in exposed and unexposed children and display trends and factors influencing the rate of reinfection. Reports of studies elsewhere by other authors are presented for comparison.

In this study the material collected on the Negro children seemed to show that the disease rose as a new infiltration in 22 out of 32 patients developing progressive pulmonary tuberculosis rather than as a breakdown of the primary focus. Mortality was high in the children who developed tuberculosis of the adult type.

In comparing the rates of reinfection tuberculosis among children who were subjected to household exposure as compared with those who were not, 428 Negro children were selected from a total of 858 because these children presented an established basic family susceptibility and, because they were not ill when found to be tuberculin positive, ensured a minimum of serious primary lesions at the beginning of the follow-up period. These were then divided into those who had and those who had not escaped further household contact. At the end of 20 years there were 4 cases in the unexposed group and 18 in the exposed group. The author concludes that superinfection does increase the risk of development of reinfection pulmonary tuberculosis.

M. F. B.

The Psychology of Medical Practice. Marc H. Hollender, M.D., Philadelphia, 1958, W. B. Saunders Co., 276 pages. Price $6.50

This book is interesting and well worth reading. Dr. Hollender, Professor of Psychiatry, State University of New York, at Syracuse, uses, as he states, the expression "psychology" to refer to the *art* of medicine, and the purpose of the text is to turn a psychological spotlight on the doctor-patient relationship. After two excellent chapters on the basic considerations and practical aspects, the text is then carried on *with* Dr. Leonard A. Stine in a discussion of the medical patient, and *with* Dr. Ernest M. Solomon in a discussion of the obstetrical. A chapter on psychological considerations in the use of drugs is one of the best in the book.

The two chapters *by* Dr. Julius B. Richmond on the pediatric patient in health and in illness are disappointing. They are distinctly academic in approach and at times somewhat pedantic. Further, they are tinctured with Freudism, although he warns against the pediatrician becoming a child psychologist. One wishes the inherent "triangle relationship" that exists in pediatrics, doctor-child-parent, had been discussed by a pediatrician of the type of the late C. A. Aldrich or Charles A. Fife of Philadelphia, who had a vast intimate experience with the interpersonal relationships involved in pediatric practice as a background. The "art" of pediatrics will always be a complicated matter to which the pediatrician must adjust in many ways, and is a subject that does not lend itself to an academic discussion with a particular school of psychological concepts as a basis.

Editor's Column

JOURNAL OF PEDIATRICS EDUCATIONAL LECTURESHIPS FOR 1959

A change from the 1958 Foreign Lectureship program will be made for 1959 due to the meeting of the International Congress of Pediatrics in Montreal in July. As a result of discussions with the Congress Program Committee and with pediatric colleagues in several foreign countries, the Foundation has decided to split the one Lectureship for one month, with the Lecturer visiting four clinics, into a number of Lectureships, each on the same basis as the Domestic Lectureships. The Foreign Lecturers will be assigned to clinics in the United States and Canada the week of July 12, the week preceding the Congress, which opens July 19, and will take part in the Congress program.

There will be four Domestic Lectureships available, as there were this year, designed to meet the particular needs of Clinics.

Full information as to the Foreign Lecturers available for next year, as well as the Domestic Lectureships, will be sent before the first of the year to Heads of University Pediatric Departments and the larger unaffiliated Children's Hospitals with a teaching program.

MULTIPLE HANDICAPS IN THE CEREBRAL PALSIED

THE cerebral palsies are basically motor disabilities resulting from cerebral maldevelopment or injury produced by a wide variety of causative mechanisms. Since cerebral function manifests itself in diverse ways, it is not surprising that associated nonmotor disabilities would also be exhibited in an appreciable number of affected children. In fact, it is the unusual child whose handicap is entirely limited to the motor field. Depending on the nature, degree, extent, and timing of the injurious mechanisms, these associated disabilities may actually be the determining factors in the eventual social adjustment of the child. Of greatest importance in this respect may be listed: mental retardation, convulsive disorders, personality defects, and language disabilities. Since the fundamental aim in the management of the child with cerebral palsy should be the eventual integration, whenever possible, into a competitive society, the necessity of stressing the implications of these associated disabilities in the over-all management program is basic to the problem. It is our purpose to review briefly some of these associated disabilities as they pertain to the cerebral palsied.

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The incidence of mental retardation among the cerebral palsied is difficult to determine, primarily because of basic deficiencies in our available testing procedures and their interpretations. As far as I know, there is no test that can be accepted as a valid indication of basic intelligence. Most so-called intelligence tests are designed to compare the past learning achievements of the subject with that of a standard group of comparable chronological age. Their validity will be directly related to the degree to which the type of living and learning experiences and opportunities of the standard group resembles that of the test subject. The manifest limiting nature of most motor disabilities on the usual and expected learning opportunities and experiences in infancy and early childhood imposes a handicap on the cerebral palsied that makes comparison with the standard group grossly unreliable. In spite of any compensating procedures that may be built into the testing process, when dealing with motor-handicapped subjects quantitative results may represent only the crudest approximations. In general, the usual intelligence tests will tend to underestimate intellectual capacity, occasionally to a striking degree. The importance of this observation lies in the fact that only too often decisions vitally affecting the future of the cerebral palsied child are based on such inadequate testing procedures.

The moral to this is obvious. Except in the case of the profound intellectual deficiencies whose recognition is readily apparent, diagnosis of intellectual status should be based, not entirely on short-term psychological testing and observation, but on a reasonable period of exposure to various learning opportunities that will afford adequate basis for evaluation. The implications involved in decisions based on such intellectual evaluation should determine the length of the observation period.

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It is difficult to generalize as to the management problems in the cerebral palsied when associated with varying degrees of intellectual defect. For those in whom the intelligence level is in the so-called "educable" range, every effort should be made, if practical, to integrate such a child eventually into the public school facilities designed for this type of mentally retarded patient. While the motor disability may complicate such an arrangement for the family, it does offer the most effective method of developing in a community framework the socializing experiences that are necessary if eventual useful, independent or semi-independent community existence is to be reached. While there are certain definite advantages to the segregation of the cerebral palsied as regards the management of the motor handicap therapeutically, it has definite disadvantages as regards eventual social adjustment in a normal society. Such segregating experiences should be limited to specific therapeutic needs and only for the periods when this is deemed necessary.

For the cerebral palsied child with more serious degrees of mental defect, the problem is basically different. While the nonmotor-handicapped, moderately retarded children in the so-called "trainable" category have at least a possibility of eventual supervised social integration, even if

limited in nature, if exposed to suitable educational and training community facilities, for those with an added motor handicap of any but the slightest degree the possibility of achieving such a goal is extremely unlikely. Home care for such a child is practical, however, and definitely helpful during the early years, even if some type of institutional care must eventually be sought. During this early period any orthopedic procedures that may minimize future custodial problems can be carried out or projected for future evaluation. This period also allows for the gradual process of orientation that all families with this problem need for better adjustment to the possibility of later separation.

In passing, I should mention a type of cerebral palsy almost exclusively confined to children with the most severe degrees of intellectual impairment, described relatively infrequently in the literature as atonic diplegia. It is by no means uncommon, however, making up about 10 to 15 per cent of our total cerebral palsy population at Southbury, Connecticut. This is characterized by a generalized flaccidity, with little spontaneous motor activity, present presumably from birth. The degree of hypotonia may be so marked as to require the differentiation from amyotonia congenita. This is easily ruled out, however, by the presence of very brisk deep reflexes, positive Babinski responses, ankle clonus, and an increased stretch reflex which is invariably found and persists. As the infant grows, the flabby, poorly developed muscles associated with practically absent spontaneous activity eventually lead to varying degrees of impaired joint mobility, especially in the knees and wrists. These children fail to exhibit any evidence of development of an ambulatory pattern and remain more or less permanently bedridden. The etiology is probably multiple in nature and in some cases undoubtedly genetically determined. Autopsies on three such cases at Southbury, except for the marked diminution in brain weight, showed remarkably few specific alterations. These consisted of a deficit in the ganglion cell population throughout the brain, including the cerebellum, with minimal abnormalities in the myelin structure. In fact, the striking disparity between the clinical and pathological findings was characteristic. Therapeutic procedures to prevent or minimize joint immobilization or flexion deformities apparently added only to the difficulties of management without significant benefit to the child. Since diagnosis of this condition is possible during infancy, a realistic parent orientation can be developed early, including the futility of the usual therapeutic procedures.

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Because so many communities throughout the country are lacking in adequate local facilities for the education and training of the mentally retarded, it is not surprising that many of the motor handicapped, even of mild degree and in the educable category of intellectual status, eventually find their way into the various residential state institutions for the mentally retarded. Wherever possible, such children should be integrated into the institutional community in all spheres of activity on the

basis of their intellectual status rather than their motor handicap. There is an unfortunate tendency in many such state institutions toward the mass management of children with motor handicaps because of administrative considerations, regardless of intellectual capacity. Such a policy will seriously handicap any effective program designed to exploit the individual capacities of the inmates and deny them the benefits of social experiences without which eventual satisfactory community adjustment becomes unlikely.

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As might be expected, the incidence of convulsive disorders among the cerebral palsied is high, probably in the range of 10 to 20 times that of the normal population. The clinical seizure manifestations, however, are similar except possibly for a higher incidence of focal seizures. The response to drug therapy, while somewhat less effective than in the idiopathic variety, yields acceptable results in almost 70 per cent of the cases.

The major problems presented by the added handicap of epilepsy is not unlike that experienced by the average epileptic of similar age. This includes first the tendency, fortunately decreasing, of excluding the affected child from the usual school program and substituting home tutoring unless there is complete seizure control, which is uncommon. The psychogenic effects on a child excluded from the type of personal contacts that school should afford is a serious handicap to normal personality development not easily overcome. A second difficulty involves the family adjustment and management practices. Where there is unrealistic fear of the seizure, per se, as a possible cause of physical injury or as a potential step in intellectual deterioration, unhealthy environmental restraints and tensions can seriously impair normal emotional development. Proper medical management and parent orientation and active efforts to resist school exclusion will meet these problems. There are certain calculated risks the epileptic child with motor handicap must take if he is to have a reasonably healthy emotional and personality development as well as improved motor function, and these must be accepted as part of the price he pays for a more effective future existence.

The effectiveness of anticonvulsant drugs in the cerebral palsied child is more or less similar to that in those not so handicapped. We feel that, in general, phenobarbital and Dilantin are still the most useful and probably the safest, in spite of the many other drugs available and constantly being tested. Undesirable side effects, however, especially with Dilantin, may occur with somewhat smaller doses in the cerebral palsied individual. Slight impairment of coordination, a common associated drug effect and easily compensated for by the normal child, may become clinically evident and undesirable in the motor-handicapped child. Closer supervision is therefore required.

Mental relaxation, motor inactivity, and mild drowsiness are definite activating mechanisms inducing increased electrical seizure discharges in the brain wave record of the epileptic individual. Our experiences suggest a similar relationship as regards overt clinical seizure activity. We have been very much impressed

by the improvement in seizure control that occurs when efforts are made to increase both mental and physical activity through broader and bolder programming wherever possible.

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Probably the most serious of the multiple handicaps resulting from organic cerebral abnormality relates to the interference with the development of basic personality structure that occasionally occurs. We here define "basic personality structure" in terms of a pattern of development that under normal conditions leads to the capacity to realize a satisfactory level of interpersonal relationships and the ability to achieve a useful and realistic conception of "self" in relation to the environment in which one lives. Depending, presumably, on the degree of impairment of certain aspects of cerebral function, the degree of personality impairment may vary from one of complete failure to develop any evidence of the ability to relate to people or to the environment (a condition designated as infantile autism) to less striking impairments which may complicate but not necessarily prevent eventual social adjustment. The management of these varying degrees of personality deficiencies presents one of the most challenging tasks for the medical supervisor. The presence of this type of handicap seriously impairs the learning capacity. In addition, the difficulty of psychotherapeutically "reaching" these children limits management esssentially to some type of environmental manipulation. As is the case with other handicapping conditions that can only be ameliorated but not cured, the basic problem in management is one of assisting the child in learning to live with his handicap and to develop behavior patterns compatible with some degree of social adjustment. Activity and educational programs depending on the degree of impairment must be provided, either in the community or in some type of residential school if necessary. Our own experience with the more serious degrees of personality disorders in those with or without motor handicaps has not been very happy as regards the possibility of prolonged community adjustment. Although management is difficult for these children even under ideal institutional conditions, the greater environmental flexibility that exists allows for a more acceptable degree of social integration. The use of tranquilizers to control some of the more disturbing behavior patterns that characterize many of those children has been of limited value in our hands. These cannot replace properly devised activity programs, which, when available, make the continued use of tranquilizers unnecessary. When such programs are absent, these drugs prove of relatively little value in the long-term care of these children. If used, the tranquilizing drugs should be prescribed in doses well below the sedative range to avoid a form of "chemical restraint" that has little therapeutic value for these children and may actually impair attempts at adjustment.

When used in its broadest concept, language disabilities related to cerebral abnormalities involve varying degrees of defects in all forms of symbolic expression. These include not only speech disorders of the expressive or receptive type, that is, the

aphasias, but also reading and writing disabilities. A language disability, even if mild in degree, may represent a formidable obstacle to satisfactory learning processes and experiences. If long unrecognized, the resulting frustrating failures in adjustment at home and school may also lead to serious emotional and behavior disorders. This obviously can only greatly complicate the management problem. Fortunately, specialized speech therapy, including remedial reading and writing, have proved successful in the majority of children with these types of language disabilities. Even children with minimal degrees of intellectual impairment can profit from these procedures, if indicated, and regain the opportunity to engage in the educational experiences previously beyond their capacity to absorb.

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In summary, an appreciable number of children presenting themselves for treatment of their motor disability will also exhibit one or more associated handicaps including mental retardation, convulsive disorder, basic personality defects, and language disabilities. For most of these children, the ultimate success or failure of their treatment will depend on the effectiveness with which the necessary therapeutic procedures for the management of these multiple handicaps can be integrated into the over-all rehabilitation program. The goal must not be the correction or amelioration of a motor deficit alone, but rather the total management of the affected child so that he can, if possible, be integrated into either a competitive or a sheltered social environment, depending on the degree of his handicap.

HERMAN YANNET